SYNTHESIS AND RESOLUTION OF PUKATEINE AND OF A CLOSELY RELATED ALKALOID.

by

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Preface.

This thesis embodies the results of synthetical work carried out in the laboratory of the Medical Chemistry Department of the University of Edinburgh during the academic years 1937-38 and 1939-39, under the supervision of the late Professor G. Barger, F.R.S.

The author wishes to express his sincere thanks to Professor G.F. Marrian of the Medical Chemistry Department of the University of Edinburgh, for his valuable advice towards the completion of this work, and to the Moray Fund of the University of Edinburgh for a grant which has defrayed the cost of materials.

Contents.

I. THEORY OF THE ORIGIN OF ALKALOIDS.

The wide occurrence of alkaloids in the vegetable kingdom makes it reasonable to assume that they must fulfil some important function in the life of the plant. Although this matter has often been discussed and investigated experimentally, it cannot be said that the solution of the problem is in sight. Heckel put forward the assumption that the alkaloids were intermediate products in the building up of protoplasm. If this is the case at all, it must be confined to a few alkaloids which are related to the protein amino-acids. The great majority of characteristic alkaloids are not capable of being assimilated by the plant, as has been shown experimentally, and where their quantity in the plant has diminished, no corresponding increase in the protein can be found.

On the other hand, the view has been expressed that the alkaloids are protective substances for the plant. This view is based on the fact that they are chiefly localised in the peripheral organs of the plant. However it is known from experiments that they do not protect the parts of the plant concerned from lower or even higher animals.

A third theory is that the alkaloids are

degradation/

degradation products and that their role is to bind part of the nitrogen of the desassimilation processes, a similar function to that of urea and uric acid in the animal body. But it is hard to conceive why the plant should build such complicated systems in order to bind one or two atoms of nitrogen only.

Nevertheless there is no doubt that the alkaloids are built from waste products. Pictet (1) was the first to suggest that the alkaloids are produced in plants in two successive stages, involving (i) the disruption of complex nitrogenous substances such as protein or chlorophyll, with the production of simple basic products, and (ii) the condensation of these simple basic products with other substances already present in the plant to the complex systems found in alkaloids.

In addition Pictet believed that the most common process taking place in the plant was the methylation of hydroxyl and imino groups by formaldehyde:

$$ROH + CH_2O \rightarrow ROCH_3 + O$$

$$R_2NH + CH_2O \rightarrow R_2NCH_3 + O$$

The methylated compounds are then able to undergo intramolecular transformations, by which a methyl group enters a ring; as example he gave the transformation of the pyrrol ring into a pyridine ring, an experiment which he carried out in his laboratory.

Since pyrrole and indole rings are to be found among the constituents of protein (proline, tryptophane) the origin of pyridine, quinoline and iso-quinoline could be accounted for.

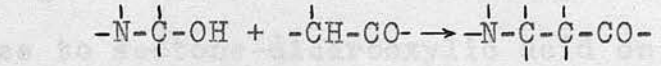
As regards the presence of simple bases in the plants, Pictet and Court (2) showed that these bases did exist, by steam distillation of carrot, tobacco, pepper, coca, parsley leaves. They were able to isolate pyrrolidine and methyl pyrroline.

Pictet's theory of transformation of pyrrole rings into pyridine has been severely criticised and the chief argument against it is that such reactions occur only at high temperatures.

More recently Robinson (3) worked out a theory which explains in the most satisfactory manner the natural synthesis of alkaloids. He showed that the initial products are formaldehyde, ammonia, ornithine, lysine and degradation products of carbohydrates. The important part played by formaldehyde had already been mentioned by Pictet; Hess pointed out that methylation of an amine by formaldehyde has at the same time an oxidising effect, so that amino alcohols are converted into methyl amino ketones (4).

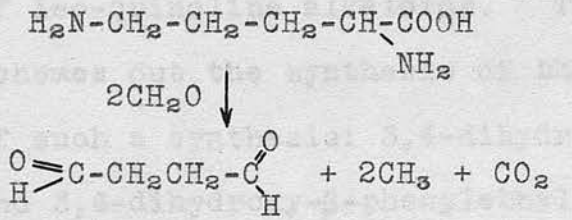
Condensation of an aldehyde or a ketone with ammonia leads to a carbinolamine; by further condensation/

condensation with the group -CH-CO-

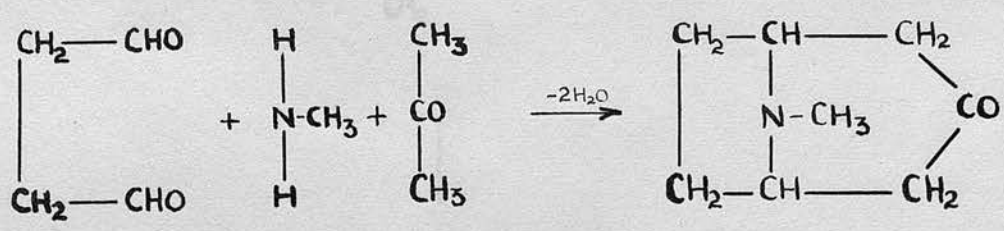


the synthesis of all alkaloids is theoretically possible.

The amino acids do not react as such; oxidation converts them first into extremely reactive products. Winterstein and Trier had already pointed out that some of these products were aldehydes. Robinson then indicated how succindialdehyde might arise from ornithine by a methylation and an oxidation:



Even though it is difficult to give the proof of such a hypothesis, Robinson's theories were supported by his synthesis of tropinone; the mechanism of this synthesis is so simple that we can well believe the plant to take a similar way: by mixing together succindialdehyde, methylamine and acetone, and allowing the mixture to stay at room temperature, he was able to detect the presence of tropinone after half an hour (3).



There are good reasons to believe that citric acid, a degradation product of carbohydrates, can give rise to acetone-dicarboxylic acid on oxidation, thus supplying the necessary acetone-complex.

By condensation of succindialdehyde, methylamine and acetone-dicarboxylic acid, Robinson obtained tropinone-dicarboxylic acid.

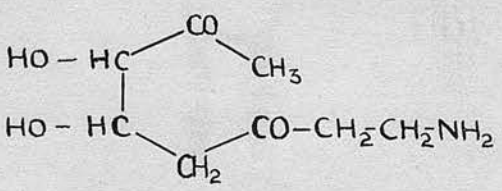
A further degradation product of a pentose or a methyl-pentose sugar is acetylglycollaldehyde (3); this aldehyde is of great interest, as this present work concerns itself with the synthesis of iso-quinoline alkaloids. This is how Robinson schemes out the synthesis of the initial products of such a synthesis: 3,4-dihydroxyphenylacetaldehyde and 3,4-dihydroxy-β-phenylethylamine, starting from ammonia, formaldehyde, acetylglycoll aldehyde and a reactive acetone derivative:

$CH_3\text{-}CO\text{-}CH(OH)\text{-}CHO + HOOC\text{-}CH_2\text{-}CO\text{-}CH_2COOH$

↓ (aldol cond.)

$CH_3\text{-}CO\text{-}CH(OH)\text{-}CH(OH)\text{-}CH_2\text{-}CO\text{-}CH_3 + CH_2O + NH_3$

↓



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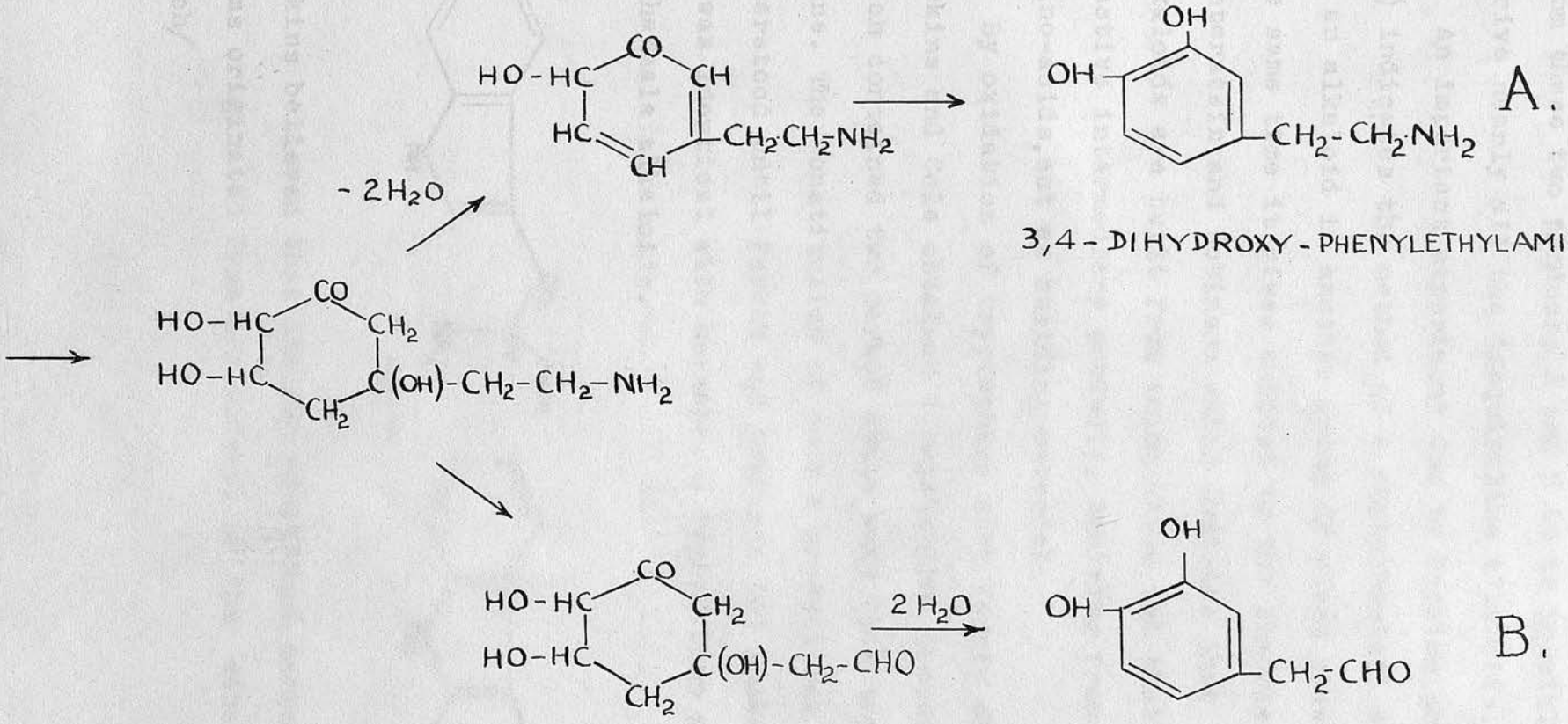
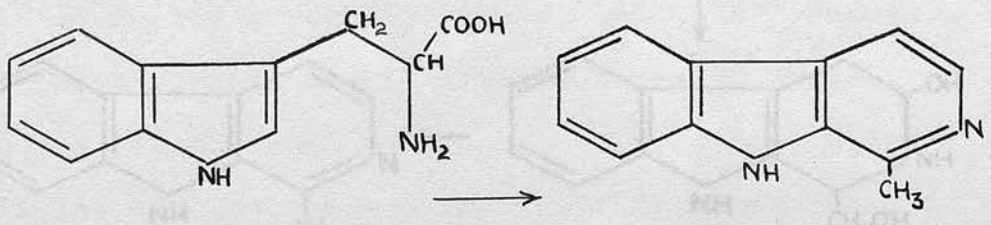

HO-HC
CO
CH
HC
CH
CH2·CH2·NH2
- 2H2O
OH
OH
CH2-CH2·NH2
A.
3,4-DIHYDROXY-PHENYLETHYLAMINE.
HO-HC
CO
CH2
HO-HC
C(OH)-CH2-CH2-NH2
CH2
HO-HC
CO
CH2
HO-HC
C(OH)-CH2-CHO
CH2
2 H2O
OH
OH
CH2-CHO
B.
3,4-DIHYDROXY-PHENYLACETALDEHYDE.

From these two products A and B it is possible to derive nearly all the isoquinoline alkaloids.

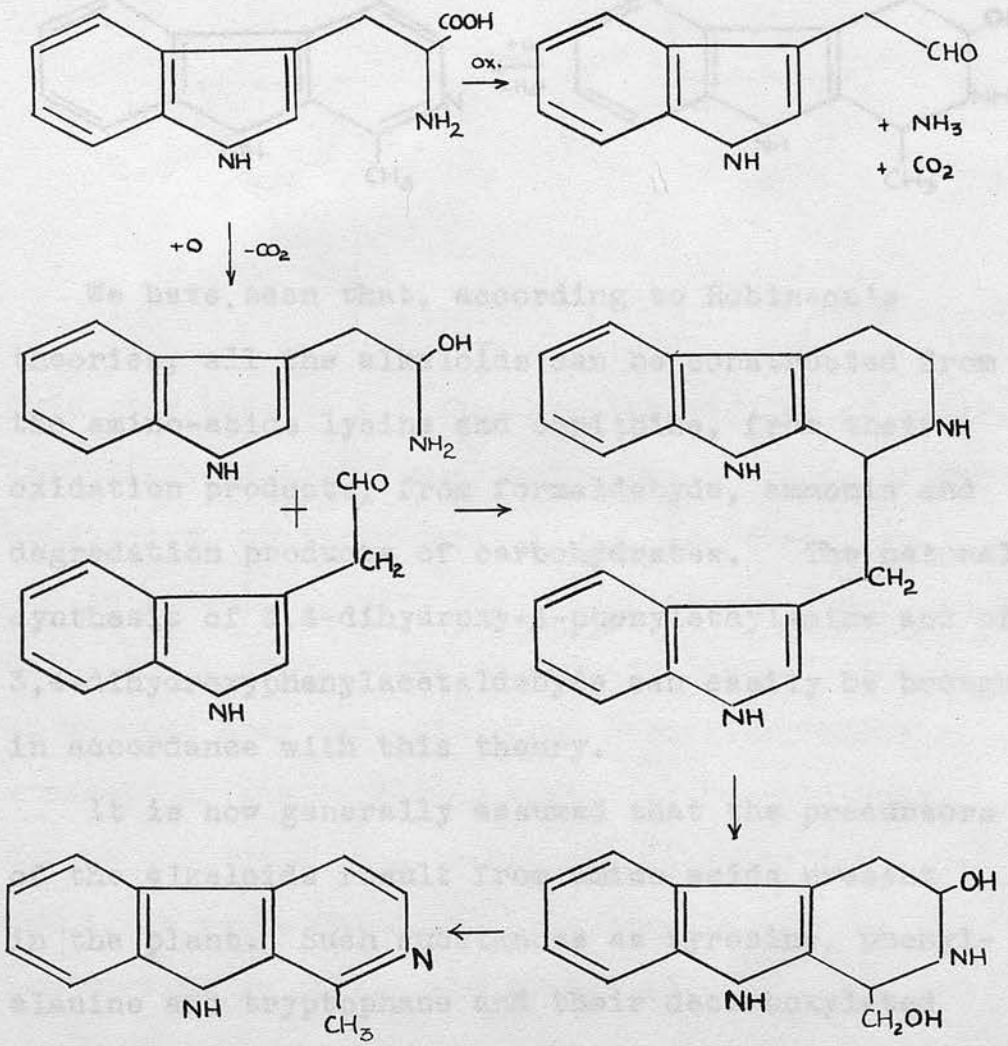
An important experiment due to Hopkins and Cole (5) indicates the method of a phytochemical synthesis of an alkaloid in another group of plant bases; at the same time it gives support to the theories of Winterstein and Robinson which indicate that alkaloids are built from amino-acids and that highly reactive intermediary products, deriving from those amino-acids, act as building-material:

By oxidation of tryptophane with ferric chloride, Hopkins and Cole obtained a crystalline compound, which contained two carbon atoms more than tryptophane. The constitution of such a product was not understood until Perkin and Robinson (6) showed that it was identical with harmane, a degradation product of harmala alkaloids.

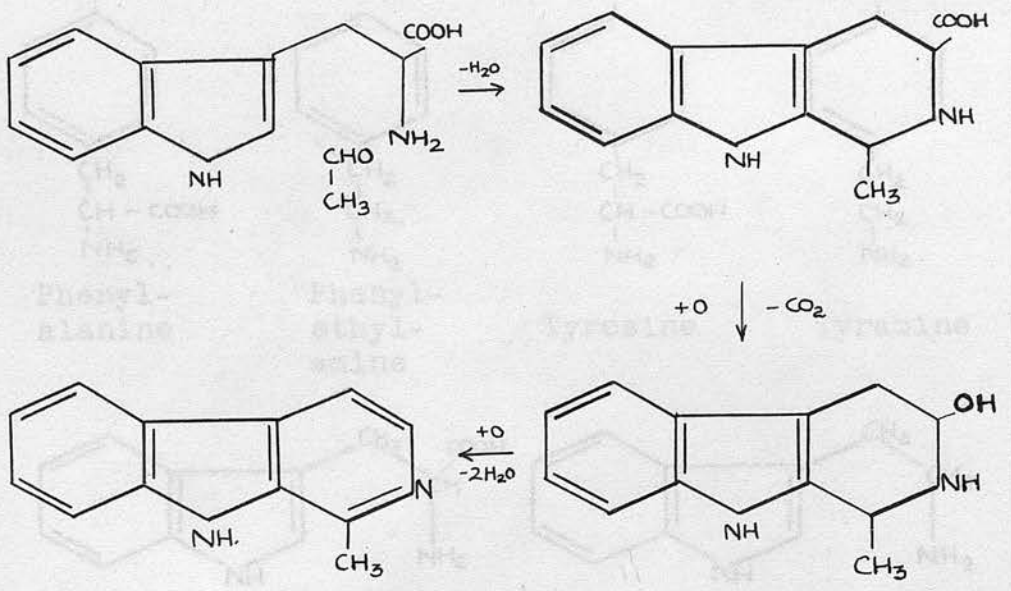


Hopkins believed that the two additional carbon atoms originated from the alcohol or the ether which/

which had been used during the oxidation of tryptophane (loc. cit.). However Robinson (6) thought this unlikely and suggested a series of reactions by which harmane could be obtained from tryptophane.

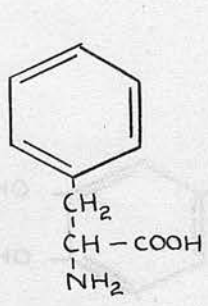


He then succeeded in obtaining harman (7) by condensation of tryptophane and acetaldehyde and oxidation of the resulting product with chromic acid, thus:

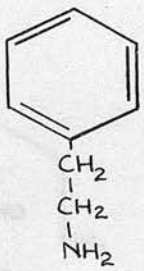


We have seen that, according to Robinson's theories, all the alkaloids can be constructed from the amino-acids lysine and ornithine, from their oxidation products, from formaldehyde, ammonia and degradation products of carbohydrates. The natural synthesis of 3,4-dihydroxy-β-phenylethylamine and of 3,4-dihydroxyphenylacetaldehyde can easily be brought in accordance with this theory.

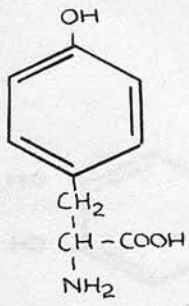
It is now generally assumed that the precursors of the alkaloids result from amino acids present in the plant. Such substances as tyrosine, phenyl-alanine and tryptophane and their decarboxylated analogues may well serve in this capacity.



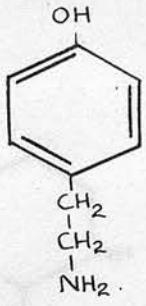
Phenyl-alanine



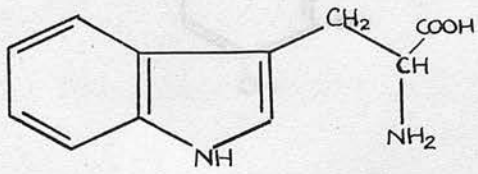
Phenyl-ethyl-amine



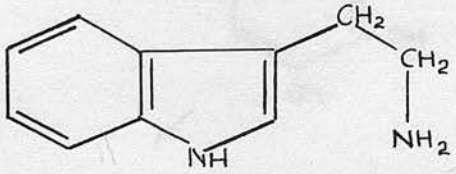
Tyrosine



Tyramine



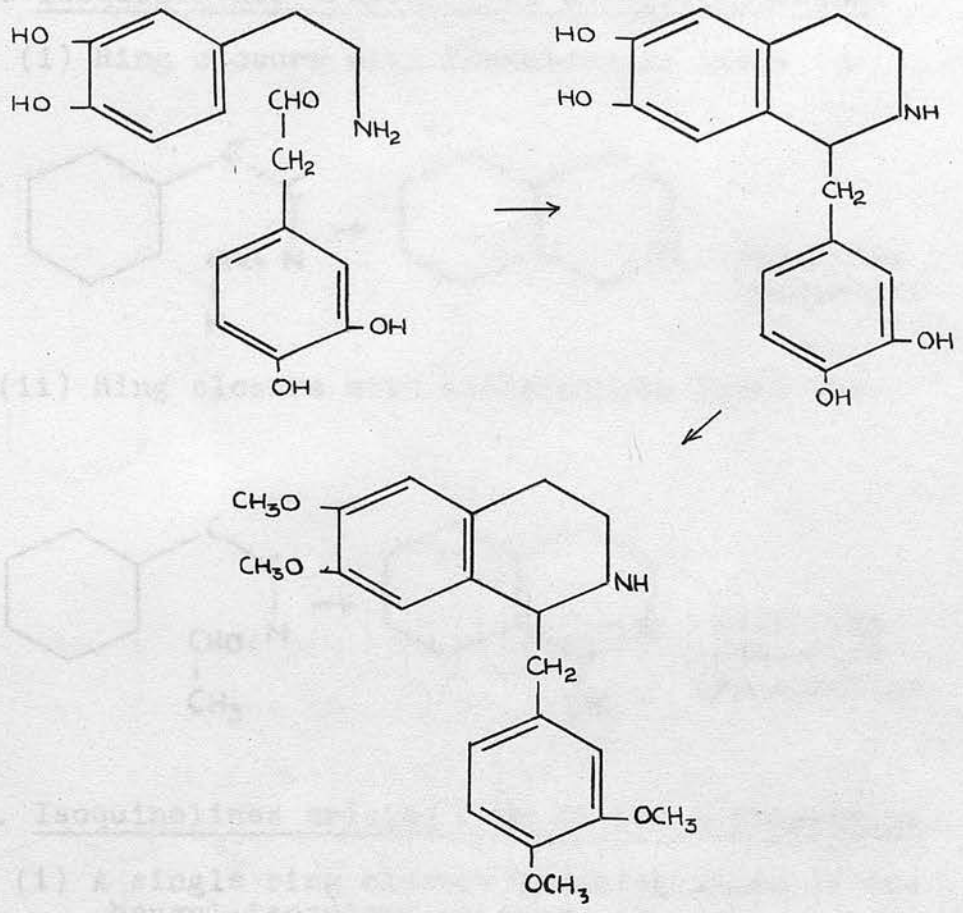
Tryptophane



Tryptamine

This view becomes all the more interesting as several investigators have demonstrated the presence of these substances, or their derivatives, in plants.

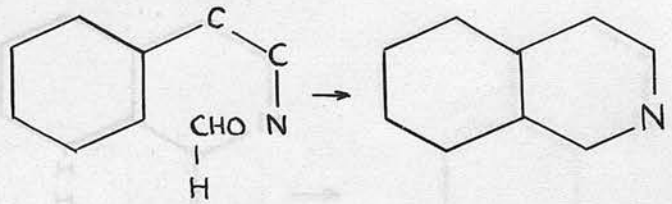
An example showing how a substituted phenylethylamine and a substituted phenylacetaldehyde, which, as we have seen may arise from phenylethylamine as a result of the oxidising action of formaldehyde, can be condensed to a tetrahydro-isoquinoline compound, is to be found in the synthesis of norlaudanosine by Spaeth and Berger (8).



Indeed nearly all the isoquinoline alkaloids may be accounted for by different ring closures which can occur between phenylethylamine and formaldehyde, acetaldehyde or phenylacetaldehyde. They may be classified as follows:

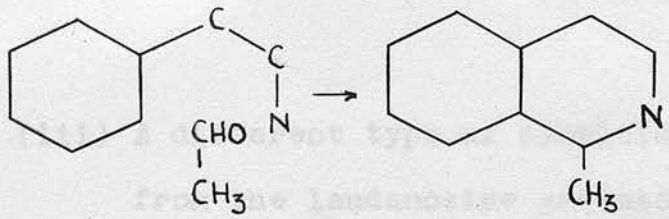
1. Isoquinolines arising from phenylethylamine.

(i) Ring closure with formaldehyde leads to:



Cotarnine
Anhalamine

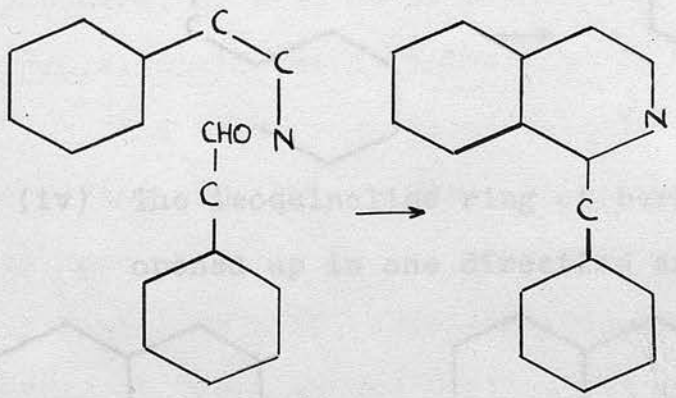
(ii) Ring closure with acetaldehyde leads to:



Pellotine
Anhalonine
Lophophorine

2. Isoquinolines arising from di-phenylethylamine.

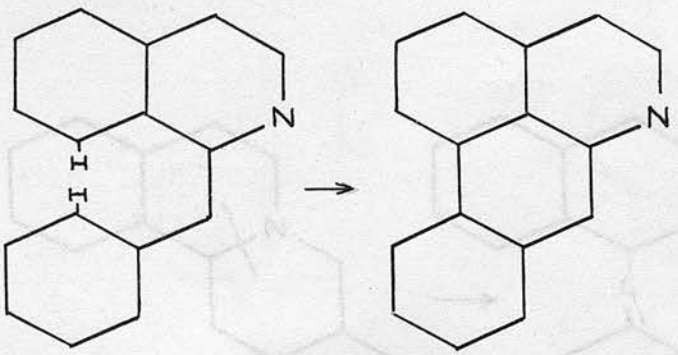
(i) A single ring closure produces bases of the benzyl-isoquinoline type:



Papaverine
Laudanosine
Laudanine

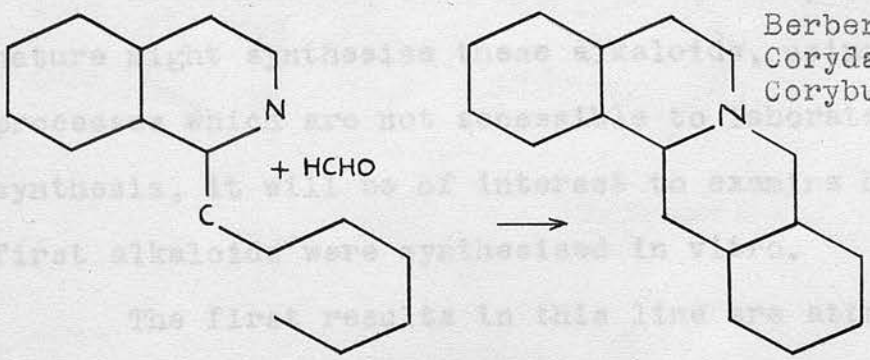
(ii) /

(ii) A second ring closure leads to the important group of the aporphine alkaloids:



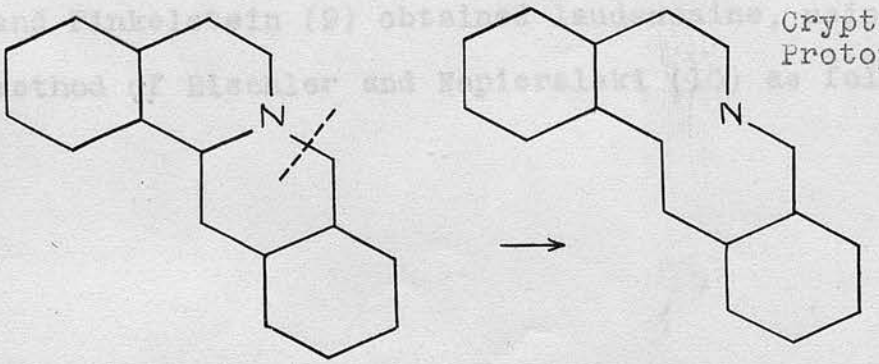
Boldine
Laurotetanine
Dicentrine
Pukateine
Laureline
Glaucine
Corytuberine
Bulbocapnine

(iii) A different type of alkaloids can be derived from the laudanosine skeleton by condensation with formaldehyde and ring closure:



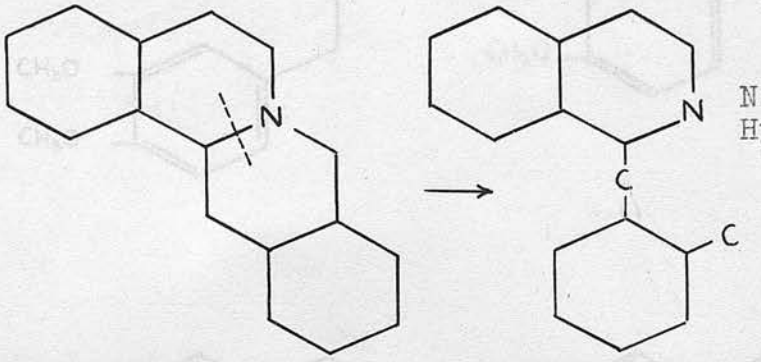
Berberine
Corydaline
Corybulbine

(iv) The isoquinoline ring of berberine can be opened up in one direction and gives:



Cryptopine
Protopine

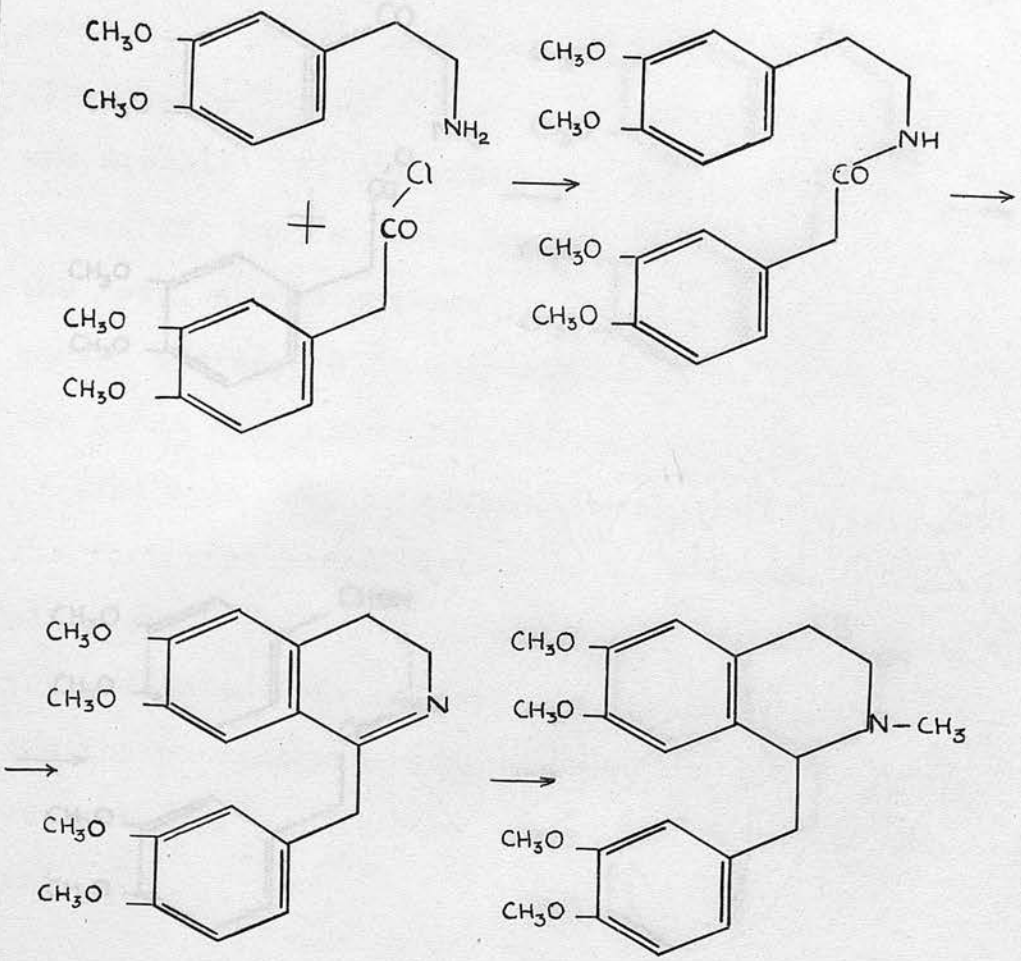
(v) Fission of berberine in another direction leads to the group of:



Narcotine
Hydrastinine

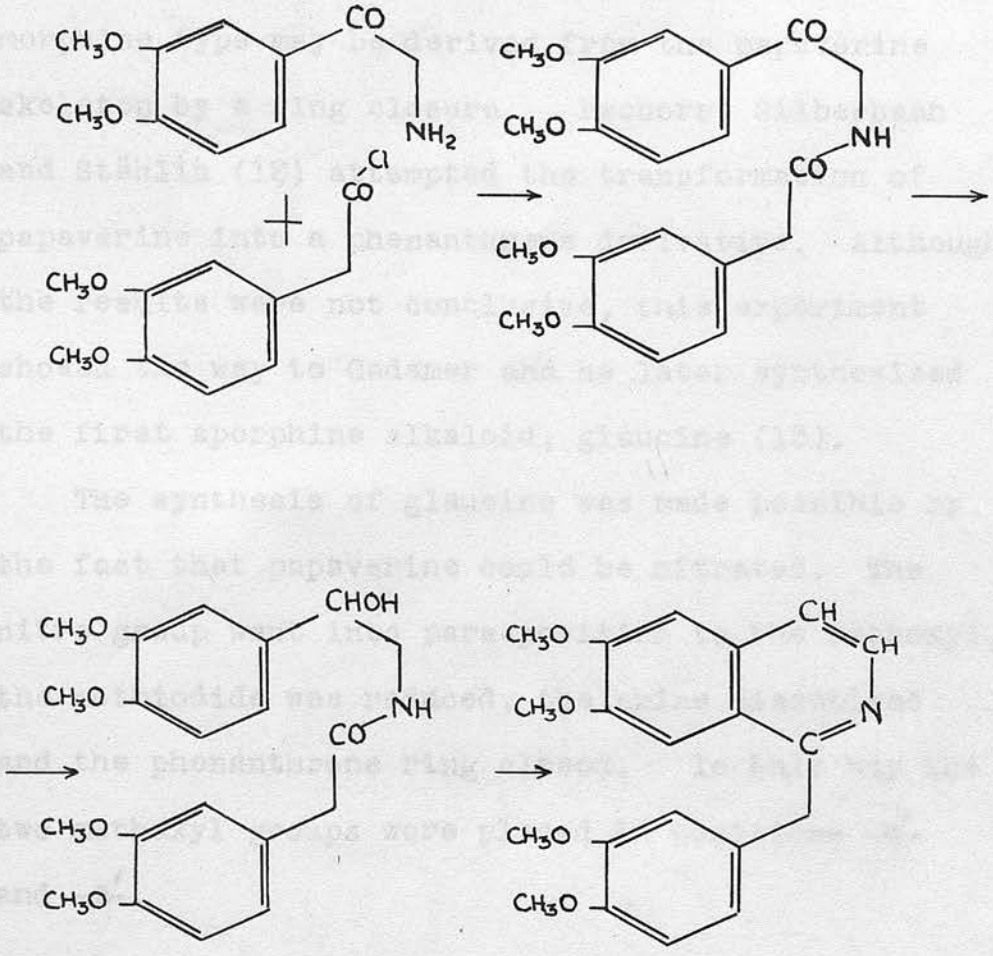
After this outline of the methods by which nature might synthesise these alkaloids, using processes which are not accessible to laboratory synthesis, it will be of interest to examine how the first alkaloids were synthesised in vitro.

The first results in this line are attributed to Pictet and the synthesis of aporphine alkaloids was made possible by the work of Pschorr. Pictet and Finkelstein (9) obtained laudanosine, using the method of Bischler and Napieralski (10) as follows:



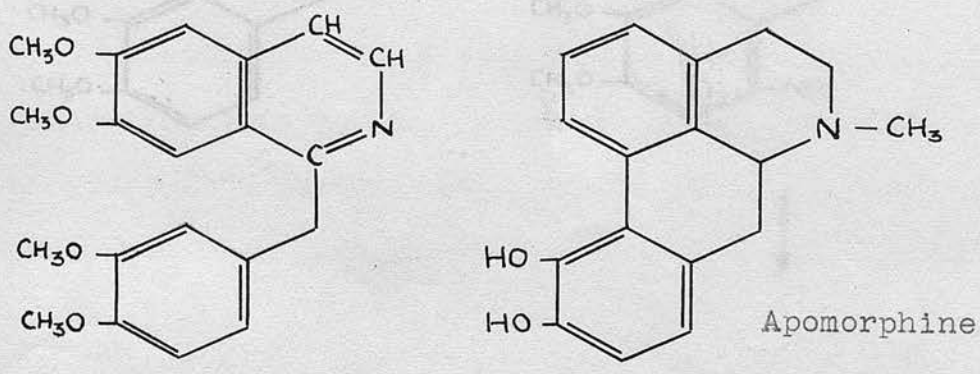
Laudanosine

Pictet and Gams (11) prepared papaverine in a similar way:



Papaverine

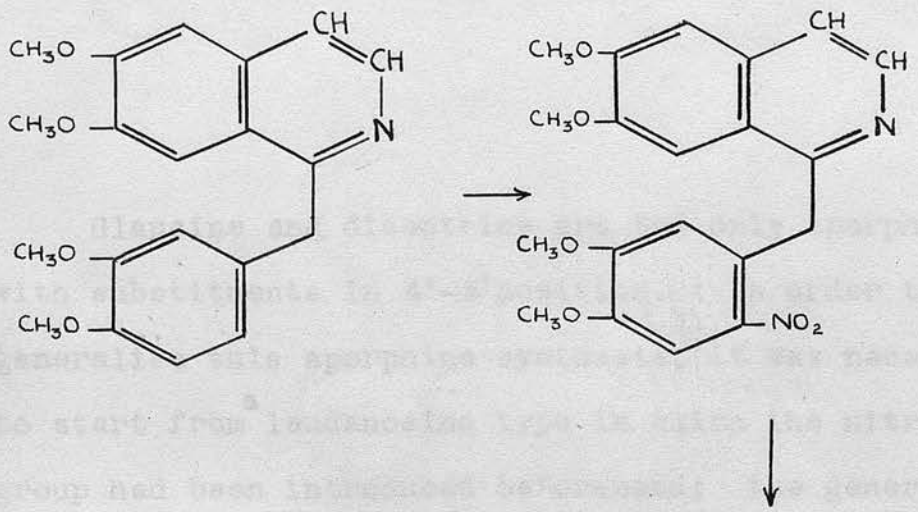
There is no doubt that the structures of papaverine and apomorphine are very similar:

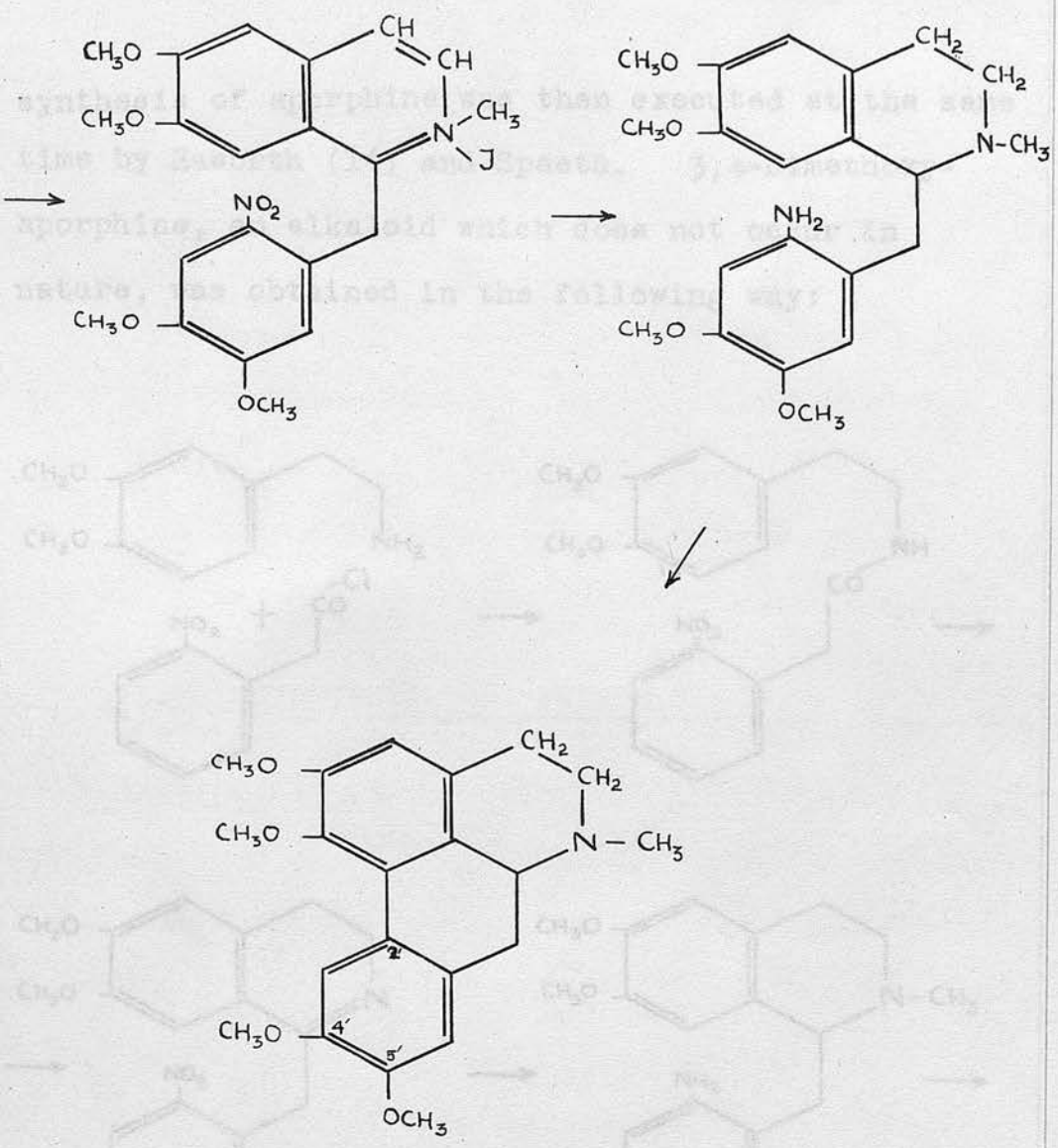


Apomorphine

and we have seen before that bases of the apomorphine type may be derived from the papaverine skeleton by a ring closure. Pschorr, Silberbach and Stählin (12) attempted the transformation of papaverine into a phenanthrene derivative. Although the results were not conclusive, this experiment showed the way to Gadamer and he later synthesised the first aporphine alkaloid, glaucine (13).

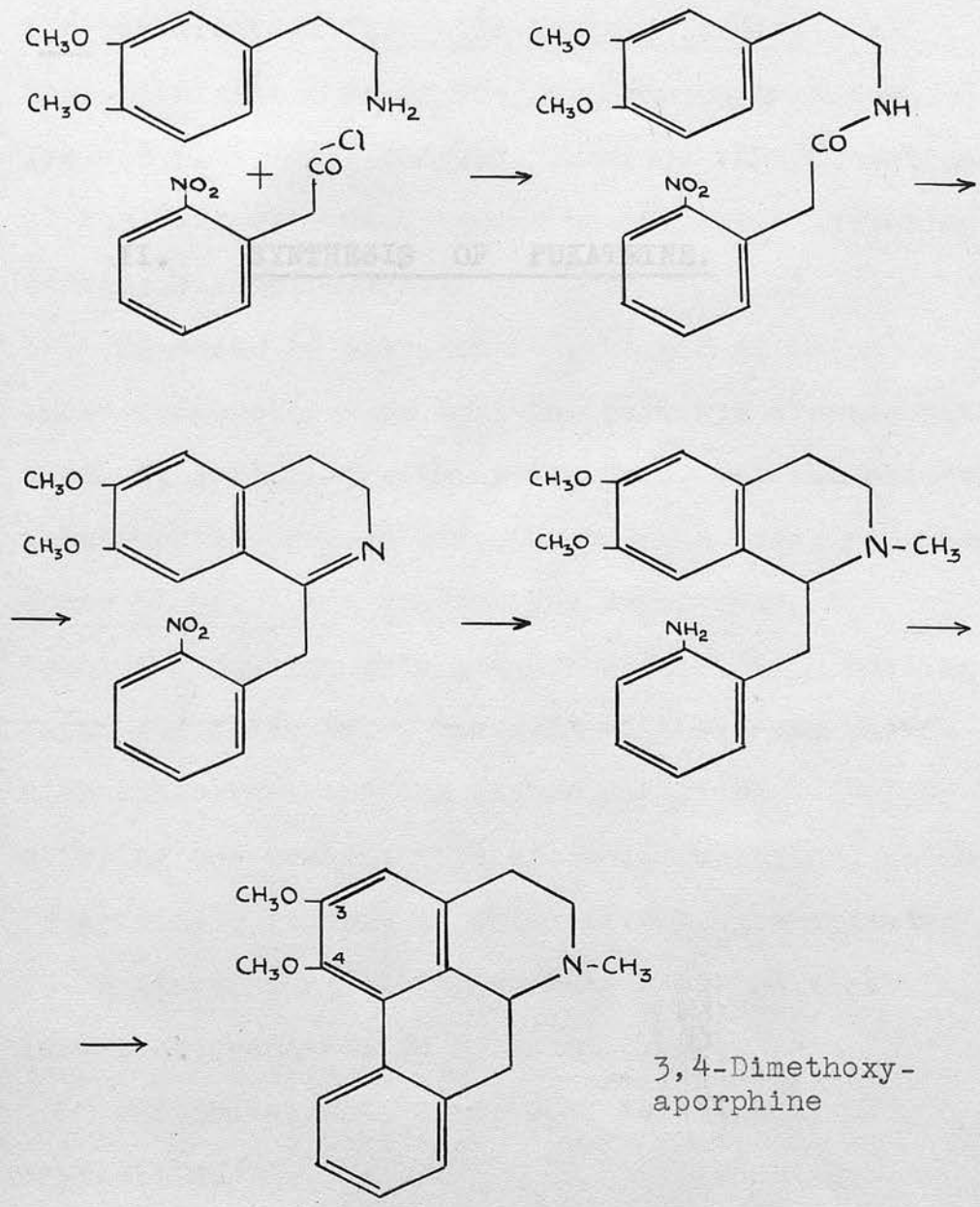
The synthesis of glaucine was made possible by the fact that papaverine could be nitrated. The nitro group went into para-position to the methoxyl, the methiodide was reduced, the amine diazotised and the phenanthrene ring closed. In this way the two methoxyl groups were placed in positions -4'- and -5'.





Glaucine and dicentrine are the only aporphines with substituents in 4'-5'position. In order to generalise this aporphine synthesis, it was necessary to start from[a] laudanosine type in which the nitro group had been introduced beforehand; the general synthesis/

synthesis of aporphine was then executed at the same time by Haworth (14) and Spaeth. 3,4-Dimethoxy-aporphine, an alkaloid which does not occur in nature, was obtained in the following way:



II. SYNTHESIS OF PUKATEINE.

II. SYNTHESIS OF PUKATEINE.

(a) Theoretical. (15)

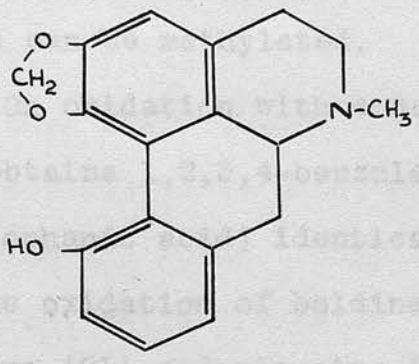
PUKATEINE has been isolated from the bark of the pukatea tree (Laurelia Novae Zelandiae), a characteristic tree of the northern part of New Zealand (16). It had been observed that decoctions of the bark were used by the Maoris for alleviating various disorders.

In order to extract the alkaloid to which these properties were due, the bark was treated with alcohol, acidified with acetic acid, and the alcohol subsequently pressed off, the process being repeated three times. The solvent was evaporated, the remaining aqueous acid liquors diluted with boiling water and filtered. The acid filtrate was shaken with chloroform and the latter distilled away. On stirring the residue with alcohol, pukateine, which is sparingly soluble in this solvent, precipitated in an almost pure state, whereas a second alkaloid, laureline, remained in solution.

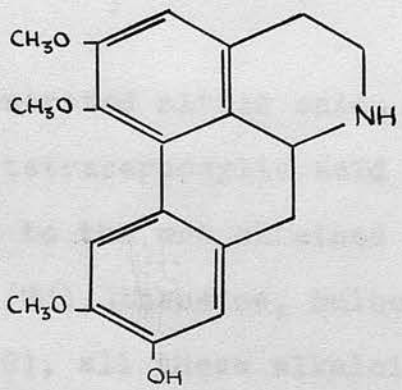
Pure pukateine, $C_{18}H_{17}O_3N$, is a white, crystalline/

crystalline alkaloid, melting at 200°, insoluble in water, sparingly so in light petroleum, more readily in ether, chloroform or absolute alcohol, and very soluble in pyridine. It is soluble in alkali hydroxide solutions and is reprecipitated on passing a current of CO_2 through the solution. It gives well crystallised salts with mineral acids.

Barger and Girardet (17), who established the constitution of pukateine, supposed that this alkaloid belonged to the Aporphine type; they had previously isolated from a plant of the family of the Lauraceae an alkaloid which they named Laurotetanine and which had aporphine structure (18). As the Lauraceae and the Monomiaceae, to which Laurelia Novae Zelandiae belongs, are in the same natural order, the authors supposed that pukateine might have the same structure as laurotetanine.



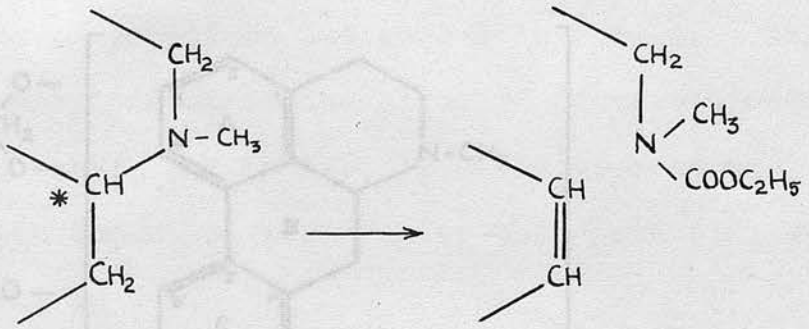
Pukateine



Laurotetanine

By/

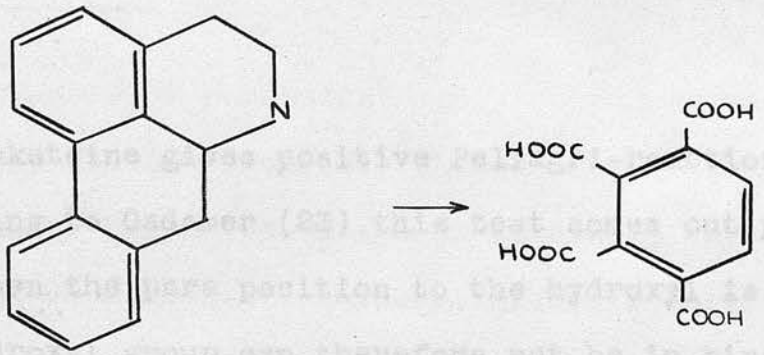
By treating the alkaloid with ethyl chloro-carbonate, they obtained a neutral and optically inactive crystalline product, which is a confirmation that the alkaloid is a derivative of tetrahydro-isoquinoline.(19)



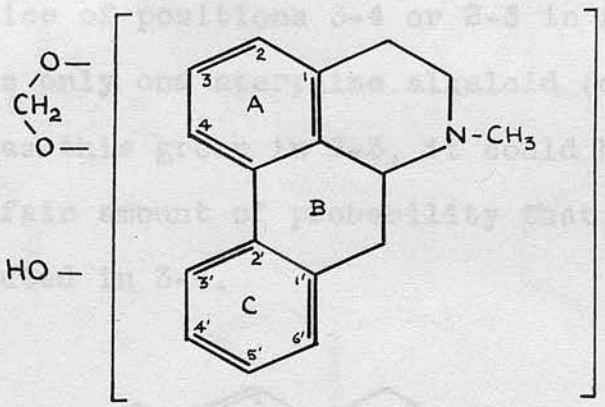
* = asymmetric C-atom

Pukateine contains a methyl-imino-group, a methylene-dioxy group and a phenolic hydroxyl, which can be methylated.

On oxidation with concentrated nitric acid, one obtains 1,2,3,4-benzole-tetracarboxylic acid (mellophanic acid) identical to the one obtained by the oxidation of boldine (20), thebaine, bulbo-capnine (21) and glaucine (22), all these alkaloids having aporphine structure.



The constitution formula of pukateine was thus supposed to be the following:



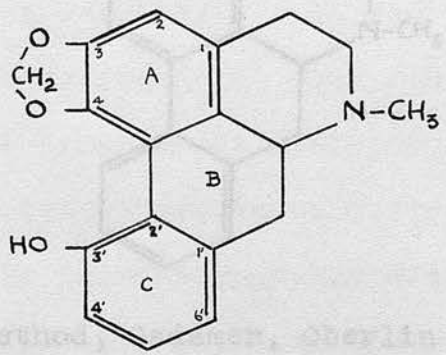
in which there remains to determine the respective positions of the methylene-dioxy group and the phenolic hydroxyl.

When the methylene-dioxy group is hydrolysed with 40% sulphuric acid, pukateine gives with ferric chloride the pyrocatechol and not the pyrogallol reaction, which indicates that the methylene-dioxy and the hydroxyl groups are in different rings.

Pukateine/

Pukateine gives positive Pellagri-reaction. According to Gadamer (23) this test comes out positive only when the para position to the hydroxyl is free. The hydroxyl group can therefore not be in ring A, and in ring C it can be in 3' or 6' only. It was assumed to be in 3' as no aporphine alkaloid has ever been found to be substituted in 6'.

As to the methylene-dioxy group, there remains the choice of positions 3-4 or 2-3 in ring A. As there is only one aporphine alkaloid (domesticine) which has this group in 2-3, it could be assumed with a fair amount of probability that pukateine was substituted in 3-4.

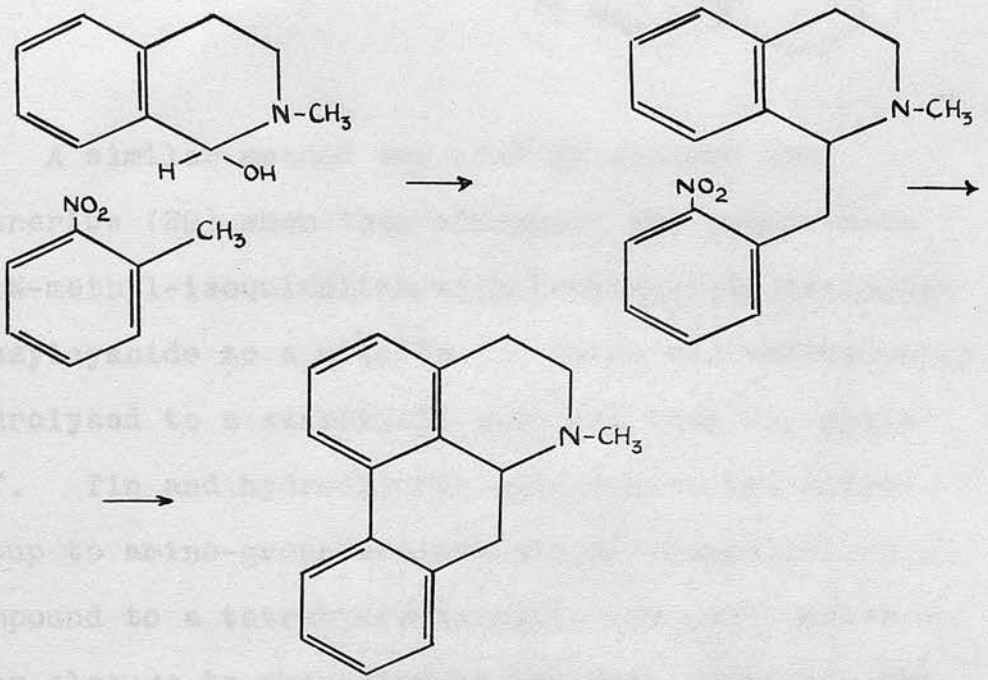


This was confirmed by the synthesis of pukateine-methyl-ether by E. Schlittler (15).

Theoretically there are several ways open for the/

the synthesis of pukateine:

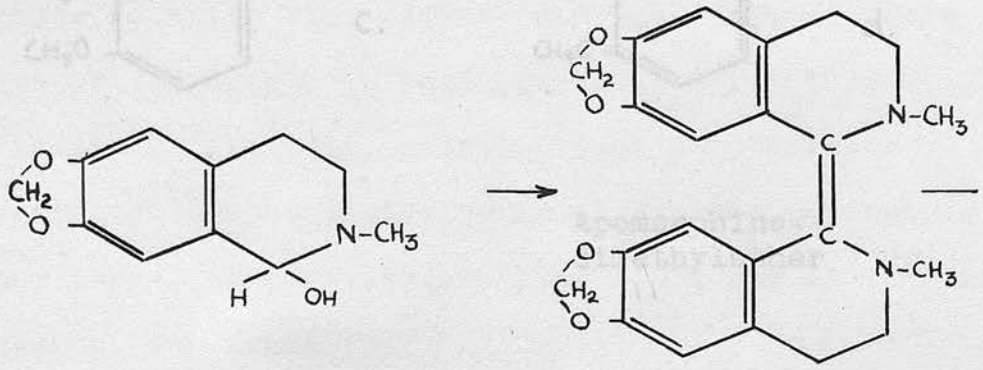
Hope and Robinson (24) showed that cotarnine and similar pseudo-bases can be condensed with derivatives of o-nitro-toluene, giving o'-nitro-benzyl-isoquinolines; the nitro group is then reduced and ring closure made to take place, following the method found by Pschorr (25).



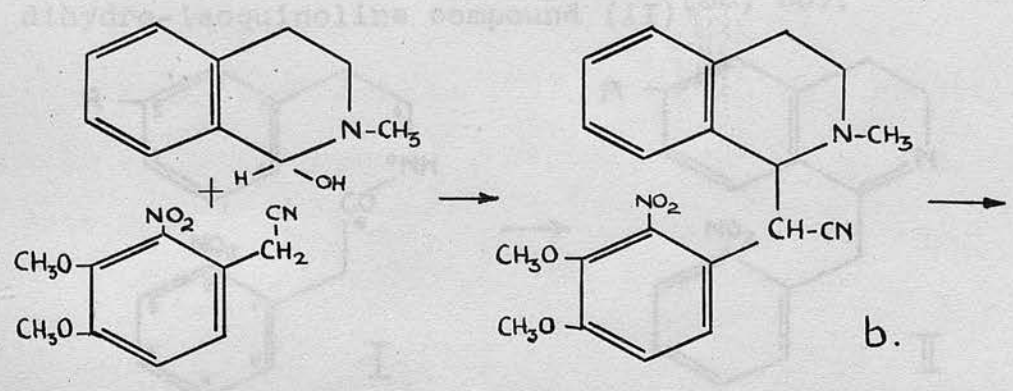
Using this method, Gadamer, Oberlin and Schoeler (26) synthesised aporphine, and Robinson (27) iso-apomorphine-dimethylether.

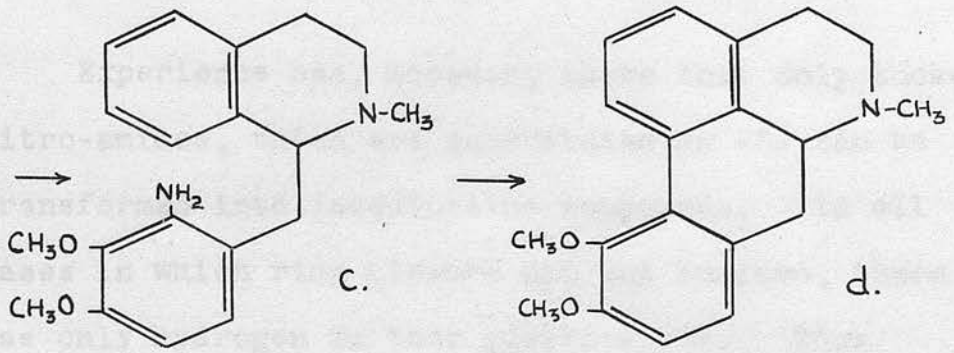
But this method is limited in its application. Robinson and Robinson (28) observed that bases of the type of hydrastinine did not condense with o-nitro/

nitro-toluene. Under the influence of sodium ethylate, they undergo an auto-condensation, forming probably a di-anhydro-dihydrastinine.



A similar method was used by Pschorr and Avenarius (29) when they condensed the pseudo-base of N-methyl-isoquinoline with 2-nitro-3,4-dimethoxy-benzylcyanide to a nitrile (b) which was subsequently hydrolysed to a carboxylic acid and then CO_2 split off. Tin and hydrochloric acid reduce the nitro-group to amino-group and the dihydro-isoquinoline compound to a tetrahydro-isoquinoline (c); after ring closure to phenanthrene had been effected, the authors claim to have obtained apomorphine-dimethyl-ether (d).

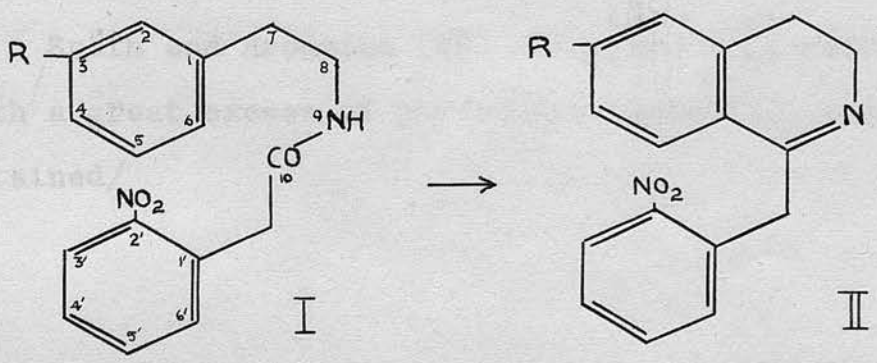




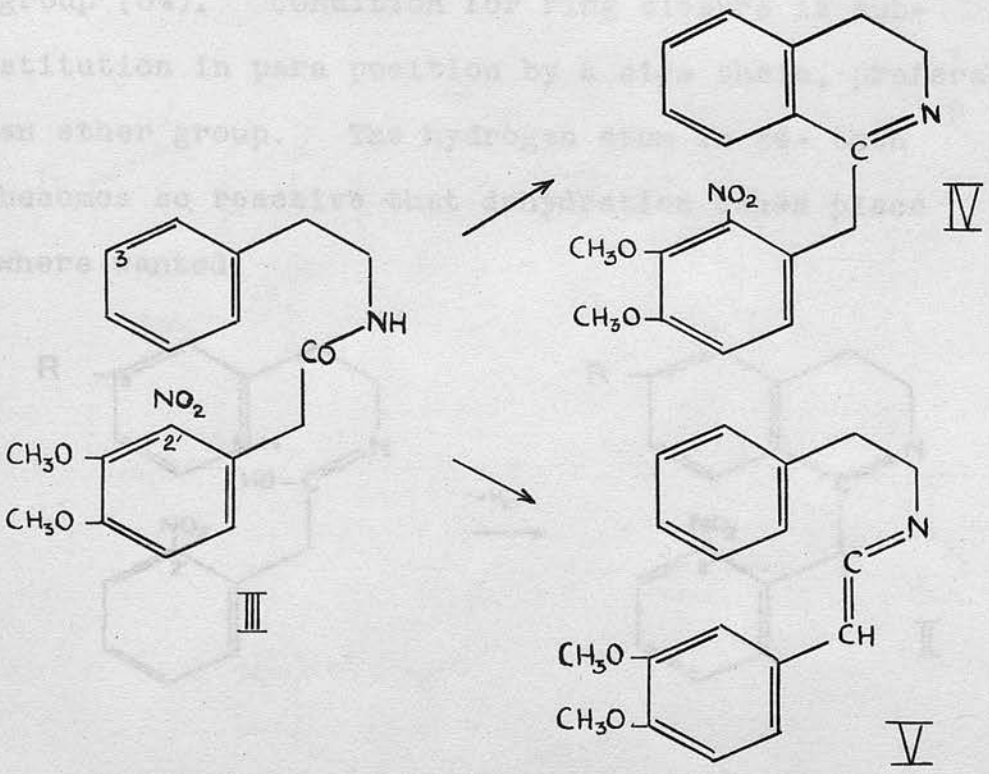
Apomorphine-
dimethylether

A third method is the one of Bischler and Napieralski. It has been used for the synthesis of many alkaloids with aporphine structure (30, 31): Pukateine was synthesised according to this method.

An acid amide (I) formed by the condensation of a substituted phenylethylamine and the acid chloride of an o-nitro-phenylacetic acid, is submitted to the dehydrating action of phosphorus pentoxide, pentachloride or oxychloride. By ring closure between positions -6- and -10- there is formation of a dihydro-isoquinoline compound (II)[32, 33].



Experience has, however, shown that only those nitro-amides, which are substituted in -3- can be transformed into isoquinoline compounds. In all cases in which ring closure did not succeed, there was only hydrogen in that position -3-. Thus Pictet and Kay (31), starting from N-(2'-nitro-veratroyl)-β-phenylethylamine (III), did not obtain any benzyl-dihydro-isoquinoline (IV), but an isomeric neutral substance (V).

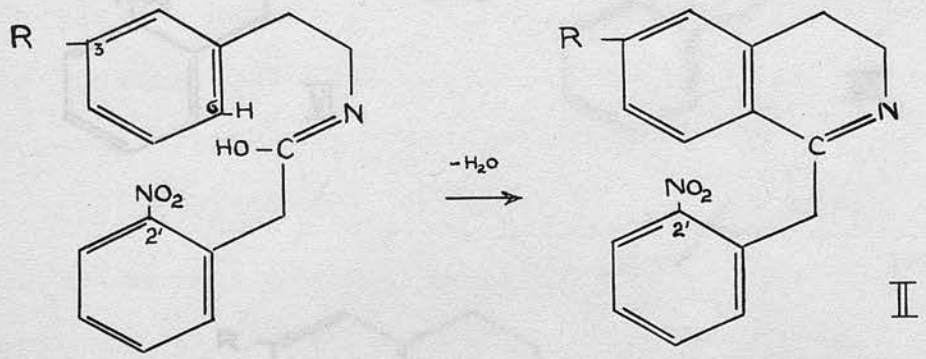


Späth and Hromatka (32) attempted this reaction with a great excess of phosphorus pentoxide, and obtained/

obtained but little basic substance.

On the other hand, if the nitro group is absent ring closure takes place readily. This shows what strong influence the 2'-nitro group exerts on the neighbouring $-CH_2$ group, water being removed from the $-CH_2-CO-NH-$ group and no isoquinoline compound being formed.

No better results are obtained if the nitro group is replaced by the amino or the acetamino group (34). Condition for ring closure is substitution in para position by a side chain, preferably an ether group. The hydrogen atom in -6- then becomes so reactive that dehydration takes place where wanted.

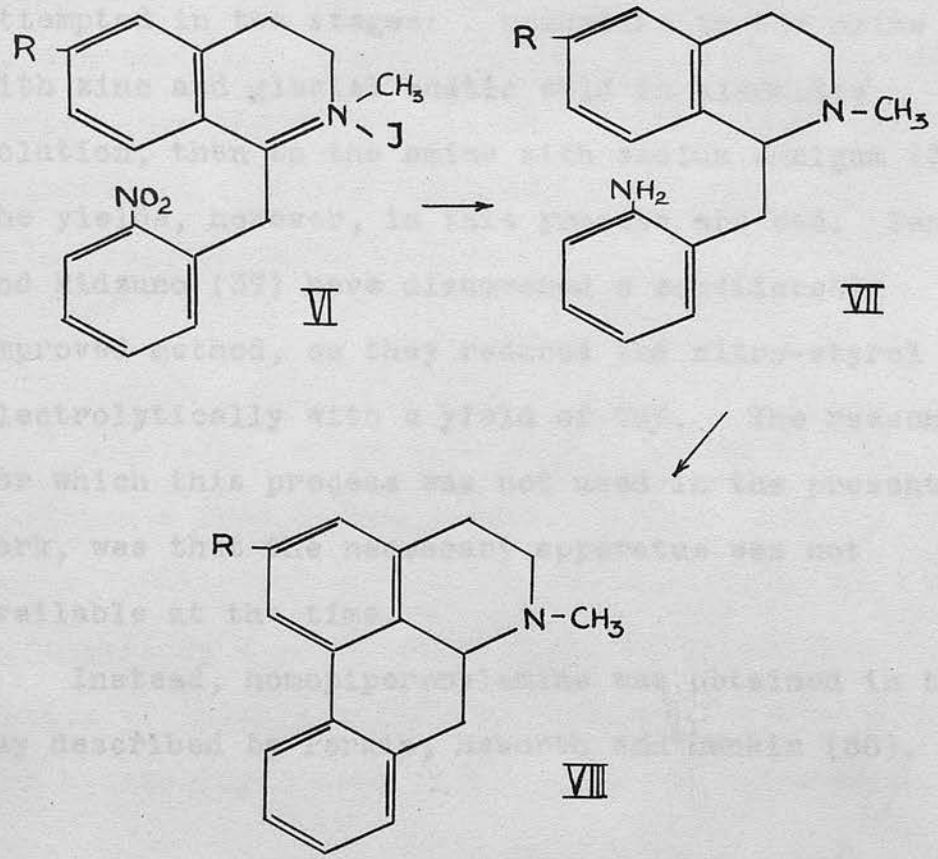


II

Of the three dehydrating agents mentioned, phosphorus pentoxide seems to have the widest field of application. Phosphorus pentachloride has, however, been used in the synthesis of pukateine and of/

of the other alkaloid, whose synthesis figures in the second part of this thesis.

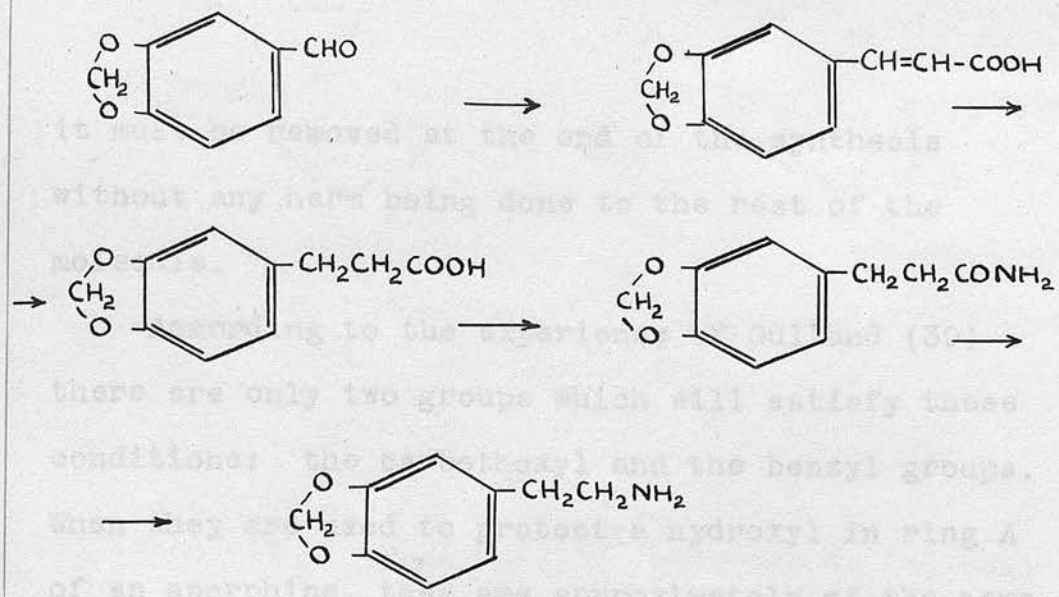
The isoquinoline base (II) is then converted into its methiodide (VI). This salt is reduced to an N-methyl-tetrahydro-isoquinoline, the nitro group being reduced at the same time (VII). The amino base is diazotised and the solution of the diazonium salt heated on the water bath, where ring closure to a phenanthrene system takes place with evolution of nitrogen (VIII).



The initial products of the synthesis of pukateine were homopiperonylamine and 2-nitro-3-benzyloxyphenylacetic acid.

HOMOPIPERONYLAMINE can be obtained in several ways. One process consists in the condensation of piperonal with nitro-methane, in presence of soda and methylamine hydrochloride, to 3,4-methylene-dioxy-ω-nitrostyrol. The yield is 98% (35). The following reduction to the amine was at first attempted in two stages: reduction to the oxime with zinc and glacial acetic acid in alcoholic solution, then to the amine with sodium amalgam (36). The yields, however, in this process are bad. Tanaka and Midzuno (37) have discovered a considerably improved method, as they reduced the nitro-styrol electrolytically with a yield of 76%. The reason for which this process was not used in the present work, was that the necessary apparatus was not available at the time.

Instead, homopiperonylamine was obtained in the way described by Perkin, Haworth and Rankin (38).



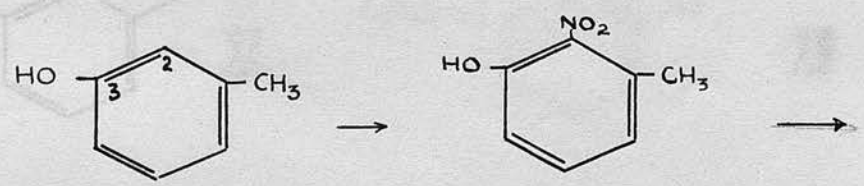
Piperonal is condensed with malonic acid in pyridine solution. The cinnamic acid is then reduced to the phenylpropionic acid by the action of sodium amalgam; the acid chloride is made and converted into the amide. Homopiperonylamine is obtained by treating the amide with sodium hypochlorite, according to Hofmann.

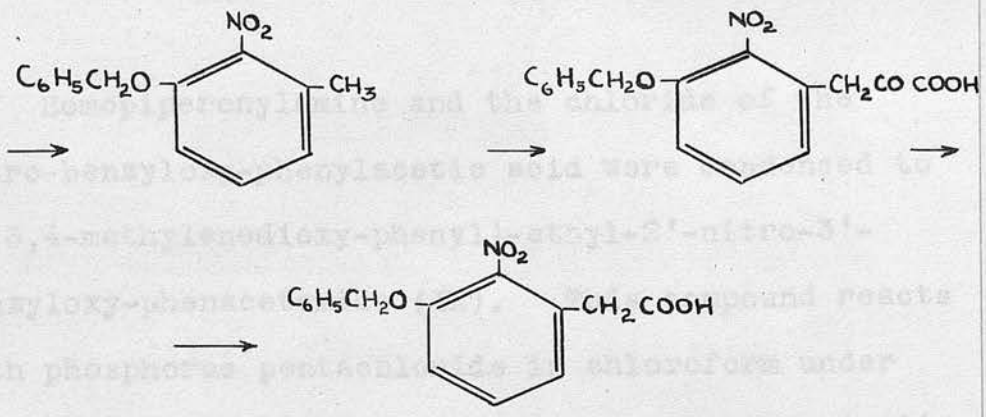
Pukateine, as we have seen, carries in -3'- position a free hydroxyl group. This hydroxyl has to be "protected" during the various stages of the synthesis by a group which shall withstand the action of thionyl chloride, phosphorus pentachloride and hydrochloric acid (1:1). On the other hand, it/

it must be removed at the end of the synthesis without any harm being done to the rest of the molecule.

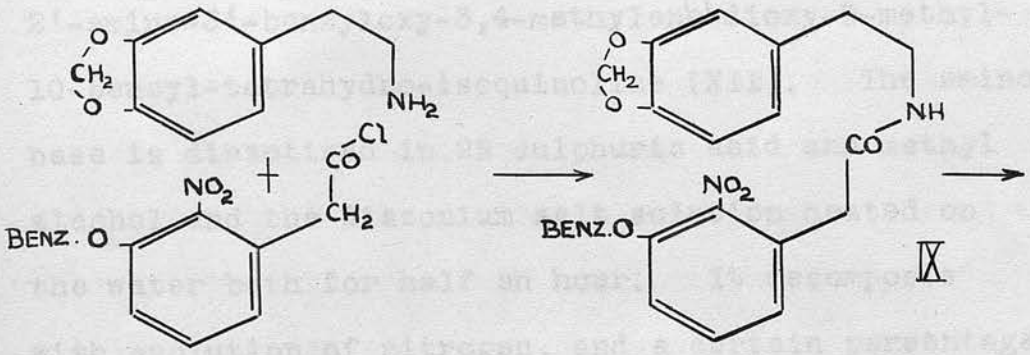
According to the experience of Gulland (39) there are only two groups which will satisfy these conditions: the carbethoxyl and the benzyl groups. When they are used to protect a hydroxyl in ring A of an aporphine, they are approximately of the same value, although the benzyl group is more stable to alkalies. The protection of hydroxyls which appear in ring C presents greater difficulties, on account of the increased susceptibility to hydrolysis of nitrated phenolic ethers. Carbethoxyl group withstands the Bischler-Napieralski ring closure but not the reduction with zinc and hydrochloric acid of the methiodide, whereas the benzyl group is stable in practically all conditions.

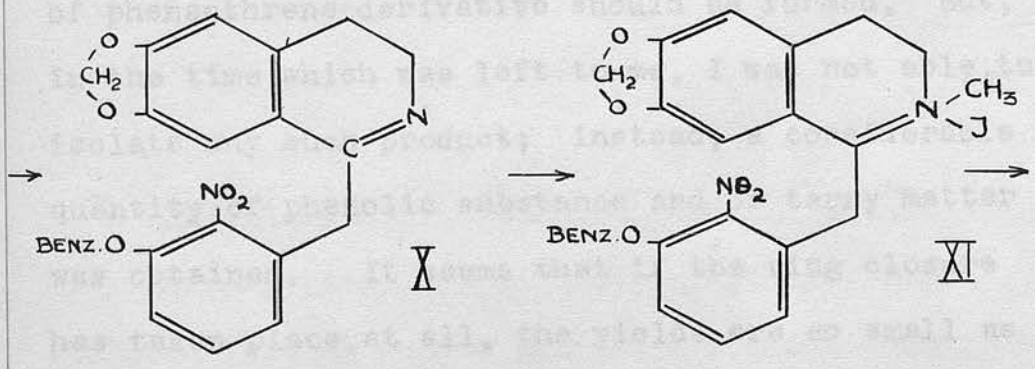
For these reasons, the benzyl group was chosen and 2-nitro-3-benzyloxy-phenylacetic acid prepared: m-cresol is nitrated in -2- position, and then benzylated. The benzylether is condensed with ethyloxalate to 2-nitro-3-benzyloxy-phenylpyruvic acid, which is finally oxidised to the corresponding phenylacetic acid with hydrogen peroxide:

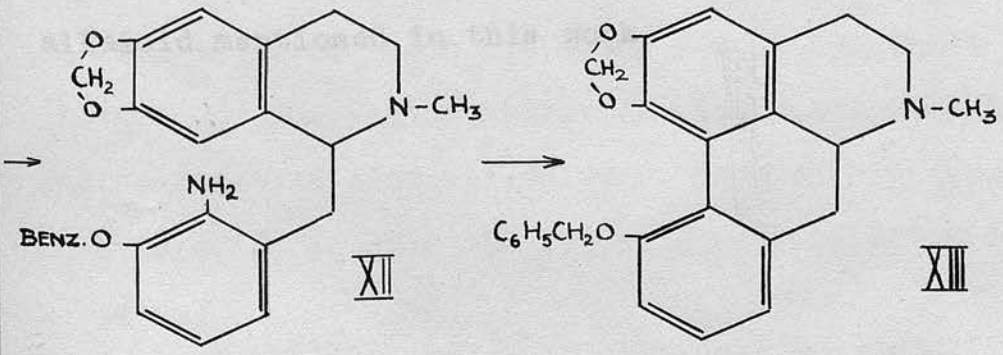




The synthesis of pukateine then proceeds as follows:







Homopiperonylamine and the chloride of the nitro-benzyloxy-phenylacetic acid were condensed to β-(3,4-methylenedioxy-phenyl)-ethyl-2'-nitro-3'-benzyloxy-phenacetamide (IX). This compound reacts with phosphorus pentachloride in chloroform under ring closure to the corresponding benzyl-isoquinoline (X), which is converted into its methiodide(XI). This is reduced with zinc and hydrochloric acid to 2'-amino-3'-benzyloxy-3,4-methylene-dioxy-9-methyl-10-benzyl-tetrahydro-isoquinoline (XII). The amino base is diazotised in 2N sulphuric acid and methyl alcohol and the diazonium salt solution heated on the water bath for half an hour. It decomposes with evolution of nitrogen, and a certain percentage of phenanthrene derivative should be formed. But, in the time which was left to me, I was not able to isolate any such product; instead, a considerable quantity of phenolic substance and of tarry matter was obtained. It seems that if the ring closure has taken place at all, the yields are so small as to be negligible, in contrast to those of the second alkaloid mentioned in this work.

(b) Experimental.

A. PREPARATION OF HOMOPIPERONYLAMINE.

1. 3,4-Methylenedioxy-cinnamic acid.[38]

Piperonal (200 g.) and malonic acid (300 g.) were dissolved in pyridine (600 c.c.) to which was added piperidine (10 c.c.) and heated on the water bath for one and a half hours. A strong evolution of carbonic acid takes place. To complete the reaction, the mixture is made to boil for 5 minutes and then poured into a large quantity of acidified water. The cinnamic acid precipitates in very small colourless needles. Recrystallised from 20% alcohol, they melt at 238°.

Yield: 228 g. = 89% of theory.

2. 3,4-Methylenedioxy-phenylpropionic acid.[40]

Mercury (4460 g.) and sodium (140 g.) were combined into 3% sodium amalgam and added during two days to a mechanically stirred solution of the cinnamic acid in water (6400 c.c.) and sodium hydroxide (50 g.). The sodium hydroxide which is formed in the reaction is neutralised every hour with hydrochloric acid, so that the solution is only slightly alkaline/

alkaline. For the last two hours the solution is heated up to 40° so as to complete the decomposition of the amalgam.

The solution is then made slightly acid; some phenylpropionic acid precipitates, together with a little quantity of tarry substance. The liquid is made alkaline again, treated with charcoal, filtered and cooled. Hydrochloric acid precipitates the acid.

Colourless needles from ligroin m.p. 84°.

Yield: 163 g. = 71% of theory.

3. 3,4-Methylenedioxy-phenyl-propionamide.(38)

The propionic acid (140 g.) was dissolved in dry chloroform (360 c.c.) and left to stand for 24 hours with thionyl chloride (106 c.c.) and then heated one hour at 40° until no more hydrochloric acid escaped. The solution was cooled and then poured, with vigorous shaking, into concentrated ammonia of d = 0.88 (1700 c.c.) which contained caustic soda (60 g.). Chloroform is distilled off in vacuo, the solution heated to 60°, some water added to dissolve ammonium chloride and the aqueous solution filtered. The amide (97.3 g.) crystallises on cooling. By extracting the mother liquors with chloroform/

chloroform, another 18.8 g. were obtained. Small colourless needles from benzole m.p. 124°. Yield: 116.1 g. = 83.5% of theory.

4. Homopiperonylamine.[41]

The Hofmann reaction was done with 10 g. amide at a time, as a larger quantity gives a considerably smaller yield. The exact quantity of chlorine was obtained by decomposing pure potassium permanganate with concentrated hydrochloric acid.

Potassium permanganate (3.27 g.) was decomposed by an excess of hydrochloric acid (1:1), the chlorine washed with water and absorbed in 10% sodium hydroxide (200 c.c.). The solution is cooled to 2° and the amide (10 g.) added with continuous shaking; the flask is heated with the hand to 20°, which takes about one hour and then gently on the water bath. At 35° practically all the amine has dissolved. The flask is then heated to 60° and after about half an hour, the first drops of amine precipitate. The solution is cooled down and caustic potash (30 g.) is added, after which the solution is heated for two hours to 50° so as to precipitate all the amine. A higher temperature causes a slight evolution of ammonia.

The/

The alkaline solution is extracted with ether, the ether in turn extracted with dilute acid; the amine is retaken in ether, dried over sodium sulphate and converted into the hydrochloride by passing gaseous hydrochloric acid through the solution.
Yield (from 110 g. amide): 58.6 g. = 51.3% of theory.

Homopiperonylamine was purified by distillation:

b.p. 132° at 12 mm.

m.p. of the hydrochloride (from absolute alcohol): 209°.

B. PREPARATION OF 2-NITRO-3-BENZYLOXY-PHENYL-ACETIC ACID.

1. 2-Nitro-m-cresole. (42)

m-Cresole (200 g.) was sulphonated at 10° with fuming sulphuric acid (8.3% SO_3)(740 c.c.) in a round-bottomed flask fitted with a mechanical stirrer. After cooling to +2° with ice-salt mixture, a mixture of fuming sulphuric acid (8.3% SO_3)(200 c.c.) and fuming nitric acid (d = 1.500) (86 c.c.) is added drop by drop during two hours; the temperature should not be allowed to rise above 5°/

5°. Thus one obtains a maximum yield of 2-nitro-cresole and the quantity of the 4- and 6-nitro isomers remains very small.

After 24 hours at room temperature, the oily liquid is divided in four portions. Each one is diluted with 200 c.c. of water and submitted to distillation with over-heated steam. The temperature of the steam should not exceed 110° for the first five minutes, to prevent any frothing. Afterwards it is raised to 160°.

The nitro-cresole distils over as a light yellow, butter-like mass, which is extracted with ether; the ethereal solution is dried over anhydrous sodium sulphate and the solvent distilled off. The nitro-cresole is a dark yellow, strongly smelling oil, which crystallises only after a very long time in the ice-box.

Yield: 197 g. = 88% of theory.

2. 2-Nitro-3-benzyloxy-toluene.(43)

2-Nitro-m-cresole (180 g.) was mixed with anhydrous potassium carbonate (230 g.). The red-orange potassium salt of the cresol forms with evolution of heat. After three hours, acetone (350 c.c.) and benzylchloride (148 g.) were added and/

and the mixture refluxed for 12 hours. The colour became pale orange. The acetone was distilled off in vacuo, and the remaining cake dissolved in a small quantity of water and the unchanged benzyl chloride blown off with steam. The benzylether was extracted with ether, the solution washed three times with water, then dried and the solvent removed. The remaining yellow oil did not crystallise, although it was thoroughly dried in high vacuum over caustic potash.

Yield: 248 g. = 82.3% of theory.

3. 2-Nitro-3-benzyloxy-phenyl-pyruvic acid.(44)

226 g. of benzylether were worked up in portions of 56.6 g. Potassium (14.1 g.) was powdered under xylene at 100°, the xylene decanted and the potassium washed three times with absolute ether. Absolute ether (460 c.c.) was added. A mixture of absolute alcohol (21.2 c.c.) and absolute ether (22 c.c.) was run in slowly. After one hour practically all the potassium had dissolved. Ethyloxalate (42.5 g.) was added to the potassium ethylate and the colour of the solution became bright yellow. It was cooled to 5° and the benzylether (56.5 g.) dissolved in a little ether, added with vigorous shaking, the colour/

colour changing from green to red. The flask was then kept at 37° for 24 hours.

Enough water was given to dissolve the dark-red potassium salt of the pyruvic acid, the aqueous layer separated and was washed twice with ether. The solution was acidified with 2N hydrochloric acid and a red oil was precipitated which became solid after some time.

4. 2-Nitro-3-benzyloxy-phenylacetic acid.(44)

The pyruvic acid was divided in four portions: each portion was dissolved in the minimum quantity of 2% sodium hydroxide, cooled down to 2° and oxidised with 20 vol. hydrogen peroxide (1200 c.c.). The colour changed from dark red to pale yellow, while considerable frothing took place.

The solution was made slightly acid and the phenyl-acetic acid precipitated as a spongy mass. It was dissolved in ether and extracted twice with 0.5 N Na_2CO_3, the carbonate solution filtered and finally carefully acidified with 2N hydrochloric acid. Thus I obtained a light yellow, crystalline precipitate of the phenylacetic acid.

The impurities which prevented the isolation of the phenylacetic acid in the first instance, were presumably/

presumably isomers from the nitration, which I had no means to remove before, as the benzylether was not stable enough to be distilled with steam. There was also a certain quantity of phenolic material produced by the fission of the benzylether.
Yield: 75.3 g. = 28.2% of theory.

The acid was recrystallised from 20% ethyl alcohol, and I obtained 59.5 g. melting at 165-166° and forming long light-yellow needles.

C. SYNTHESIS OF PUKATEINE.

1. β-(3,4-Methylenedioxyphenyl)-ethyl-2'-nitro-3'-benzyloxy-phenacetamide.

Recrystallised 2-nitro-3-benzyloxy-phenylacetic acid (59.5 g.) was dissolved in chloroform (1320 c.c.) and provided with thionyl chloride (153 g.). The flask was heated on the water bath at 50° for 3 hours, by which time the evolution of hydrochloric acid had ceased. Chloroform and thionyl chloride were distilled off in vacuo and the acid chloride, a brown-violet crystalline mass, left two days in vacuo over caustic potash, in order to absorb the last traces of $SOCl_2$.

On/

On the other hand, homopiperonylamine hydrochloride (43.8 g.) was decomposed and the base thoroughly dried. It was dissolved in dry benzene (595 c.c.). To this solution, the acid chloride, in a little benzene, was added while the flask was well shaken and cooled under the water tap. After one hour, during which the flask was frequently shaken, normal potassium hydroxide solution (230 c.c.) was given to neutralise the hydrochloric acid produced during the condensation.

The benzolic solution was separated from the aqueous layer, heated gently on the water bath and filtered. The benzene was evaporated and the crude amide crystallised as a brown mass.

Yield: 64.5 g. = 66% of theory.

The amide was recrystallised from methyl alcohol, and I obtained 54.6 g.

Bunches of colourless fine needles m.p. 132-133°.

Analysis: 4.168 mg. gave 10.136 mg. CO_2 and 1.933 mg. H_2O

= 66.36% C; 5.19% H.

Calculated for $C_{24}H_{22}O_6N_2$: 66.45% C; 5.07% H.

2./

2. 2'-Nitro-3'-benzyloxy-3,4-methylenedioxy-10-benzyl-7,8-dihydro-isoquinoline.

50 g. of the amide were divided into ten portions of 5 g. each and worked up separately; a small quantity at the time seemingly improving the yield.

The amide (5 g.) was dissolved in chloroform (70 c.c.). The mixture was well cooled, phosphorus pentachloride (6 g.) added and left in a sealed bottle for 48 hours, with frequent shaking. The phosphorus pentachloride dissolves and after a day the hydrochloride of the base began to precipitate. Chloroform and phosphorus oxychloride were evaporated in vacuo and the remaining yellow cake heated for one hour at 50° and 15 mm. pressure. Ice was given to decompose the PCl_5 in excess and the cake extracted with 700 c.c. of boiling water. The aqueous solution was filtered and, while still hot, made alkaline with ammonia.

Yield: 27.5 g. = 57.5% of theory.

Pale yellow needles from 95% alcohol, m.p. 155-156°.

Analysis: 4.996 mg. gave 10.861 mg. CO_2 and 2.124 mg. H_2O = 59.30% C; 4.89% H.

Calculated for $C_{24}H_{20}O_5N_2$: 59.40% C; 4.95% H.

3./

3. Methiodide of isoquinoline compound.

The base obtained above (25.5 g.) was dissolved in methyl alcohol (50 c.c.) and refluxed with methyl iodide (64 c.c.) for 4 hours. The bright yellow crystalline methiodide was extracted for 24 hours with absolute ether in a Soxhlet extractor, in order to remove some tarry substance and any unmethylated base.

The methiodide was recrystallised from methyl alcohol and gave bunches of pale yellow, very fine needles.

Yield: 27.9 g. = 81.5% of theory. m.p. 223°.

Analysis: 5.185 mg. gave 2.160 mg. H_2O and 10.270 mg. CO_2
= 4.66% H; 54.02% C.

Calculated for $C_{23}H_{25}O_5N_2I$: 4.30% H; 53.66% C.

4. 2'-Amino-3'-benzyloxy-3,4-methylenedioxy-9-methyl-10-benzyl-tetrahydro-isoquinoline.

The methiodide (25.85 g.) was dissolved in methyl alcohol (600 c.c.) and in a mixture in equal parts of concentrated hydrochloric acid and water (960 c.c.). Zinc dust (80 g.) was added gradually during three hours. The solution becomes practically colourless and there was formation of a grey/

grey crystalline precipitate.

Methyl alcohol is evaporated in vacuo and the solution extracted six times with ether, then made strongly alkaline and at the same time well cooled. The zinc dissolves as zincate. The amino base is extracted with ether, dissolved in dilute hydrochloric acid and re-extracted with ether, which is dried over anhydrous sodium sulphate and evaporated. The amino base remains as a red oil which does not crystallise, but gives well crystallised sulphate and hydrochloride.

Yield: 13.4 g. = 72% of theory.

m.p. of hydrochloride: 189-190°.

Analysis: 4.662 mg. gave 11.347 mg. CO_2 and 2.464 mg. H_2O

62.95% C; 5.95% H.

Calculated for $C_{25}H_{28}O_3N_2Cl$: 63.15% C; 5.89% H.

5. Racemic pukateine-benzylether.

Twice recrystallised di-hydrochloride of the precedent amino base (9.1 g.) was divided in portions of 1.5 g. The di-hydrochloride (1.5 g.) is dissolved in 2N hydrochloric acid (40 c.c.) and methyl alcohol (40 c.c.) and diazotised with the equivalent of 0.5 N. sodium nitrite at 0°. The solution becomes red with the first drops of nitrite. When the diazotation is completed, the flask is heated on the water bath for half an hour, during which a considerable evolution of nitrogen takes place. The solution became very dark red and a considerable amount of tarry matter was formed.

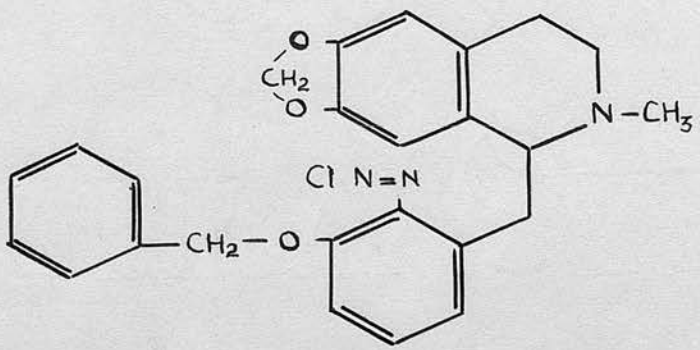
The solution is provided with concentrated hydrochloric acid (12 c.c.) and zinc dust, and reduced during half an hour. It is then cooled, make alkaline and extracted with ether. The basic substances contained in the ether are dissolved in 0.5N hydrochloric acid; the acid solution is dark red, and tarry matter precipitates again. The bases are re-extracted with ether and then dissolved again in a small quantity of 2N hydrochloric acid. This is made very nearly neutral with dilute ammonia solution and a great excess of concentrated potassium bromide solution poured in.

Although/

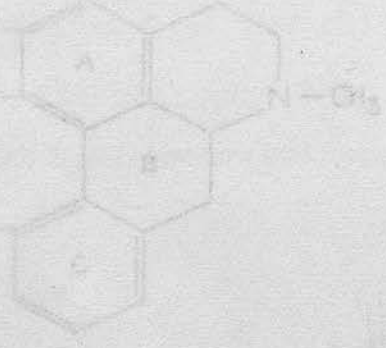
Although the mixture was left for 3 days in the ice-box, no hydrobromide of the racemic alkaloid precipitated. A second attempt with the same quantity of di-hydrochloride was equally unsuccessful.

Another 3 g. of the dihydrochloride were diazotised in the same way and the decomposition of the diazonium salt attempted with the aid of copper powder (0.5 g.). Although the evolution of nitrogen was accelerated, the results were negative, as in the first instance.

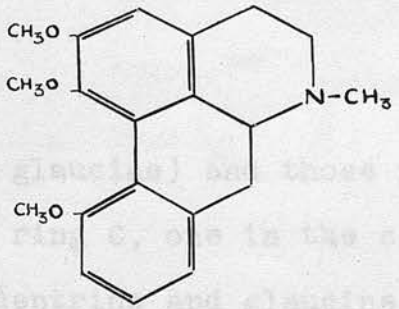
There is a possibility that the failure of a ring closure to a phenanthrene compound taking place may be due to steric hindrance by the benzyloxy group in ortho position to the diazonium chloride group.



III. SYNTHESIS OF A CLOSELY-RELATED ALKALOID.



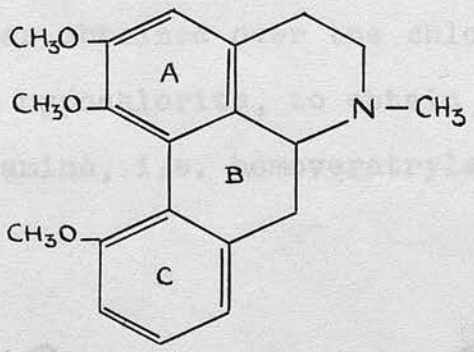
SYNTHESIS OF



(a) Theoretical.

The synthesis of this alkaloid was given to me as a subject for the second part of my work by Professor Barger. Owing to his sudden death, I was unable to ascertain the reasons for which he wished that alkaloid to be synthesised, nor did an examination of the available papers throw any light on the subject.

This alkaloid has not been found in nature, but its constitution shows plainly that even though

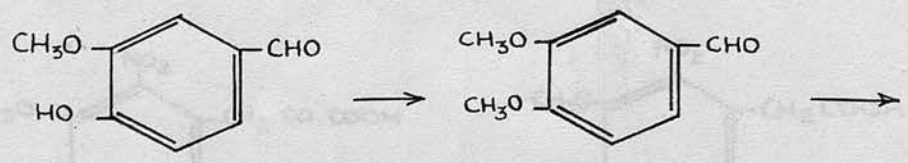


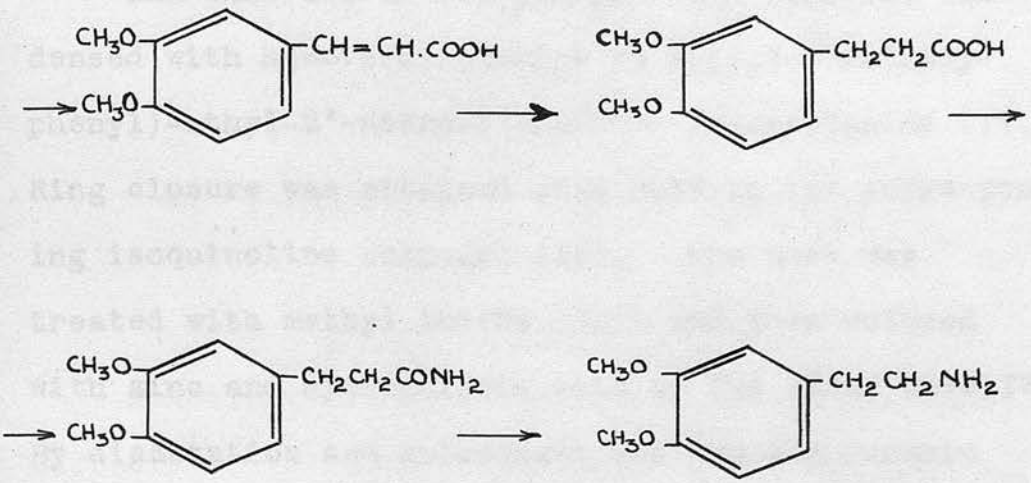
it does not exist, it might be found one day; for indeed it takes a medium position between the alkaloids with two methoxyl groups in ring A (corytuberine/

corytuberine, corydine, glaucine) and those which have methoxyl groups in ring C, one in the case of laureline and two in dicentrine and glaucine.

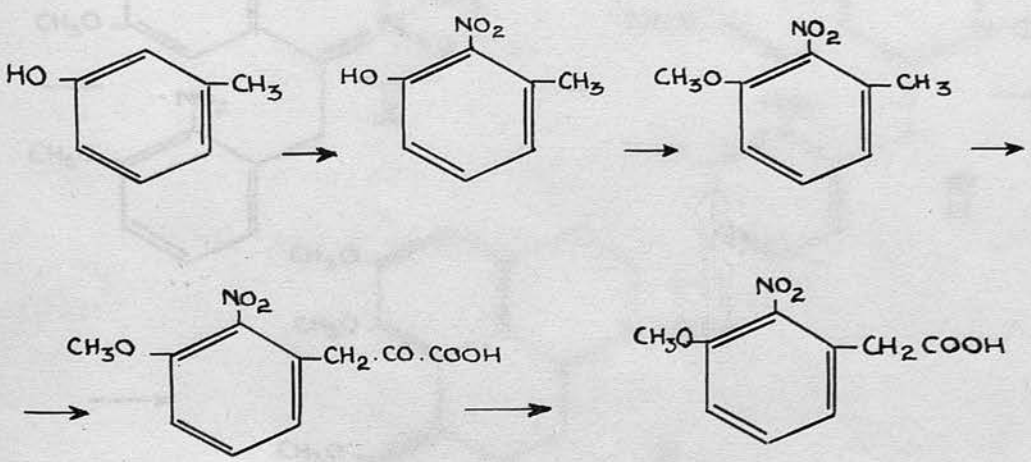
The synthesis of this alkaloid was conducted on the same lines as the one of pukateine. I started from homoveratrylamine and from 2-nitro-3-methoxy-phenylacetic acid. The fact that this phenylacetic acid carries a methoxyl group and not a benzyl group, as in pukateine, made the synthesis much easier, as there was no fission to be feared.

HOMOVERATRYLAMINE was obtained in the following way: Vanillin was methylated, then condensed with malonic acid to 3,4-dimethoxy-cinnamic acid, which was reduced to 3,4-dimethoxyphenylpropionic acid. The amide was obtained over the chloride and treated with sodium hypochlorite, to obtain 3,4-dimethoxy-phenylethylamine, i.e. homoveratrylamine.

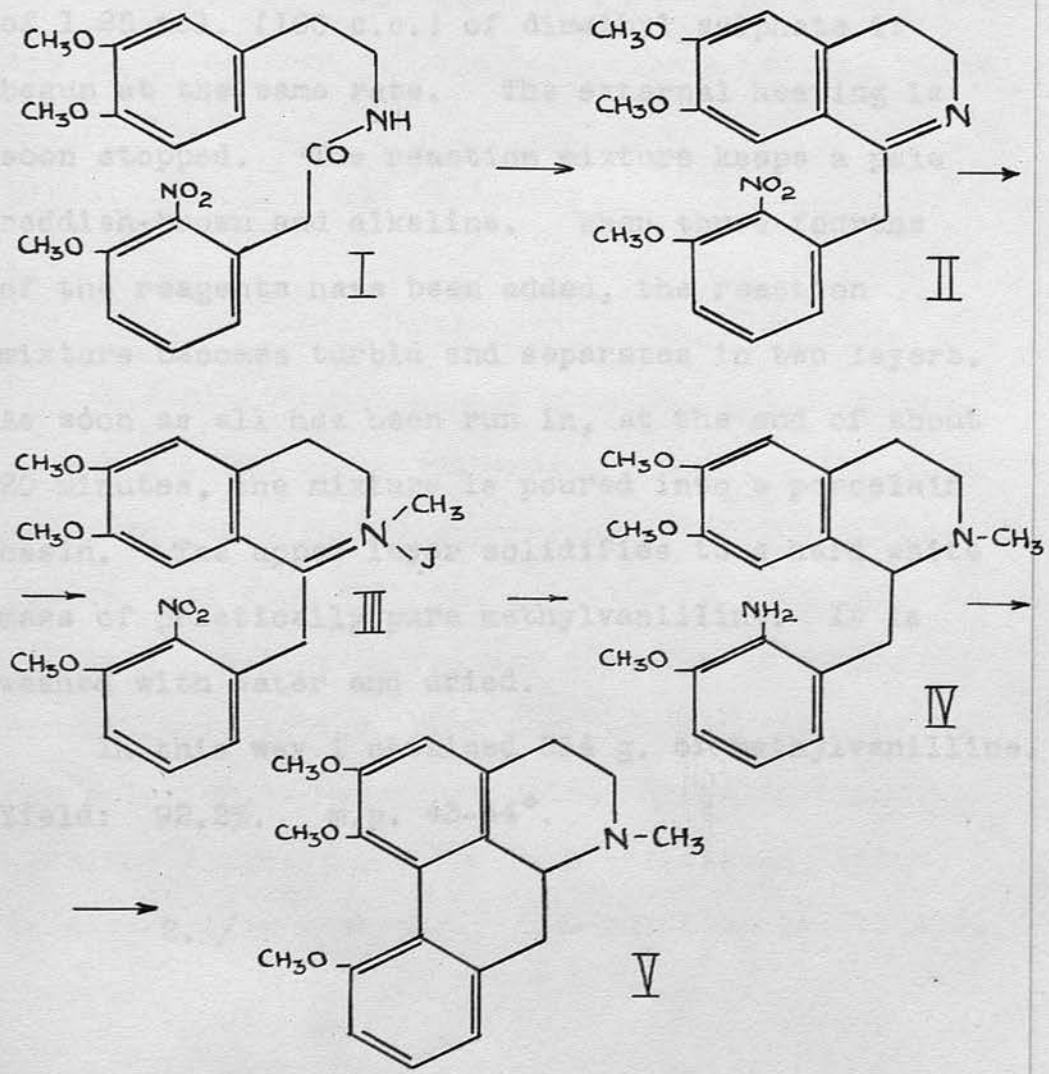




2-NITRO-3-METHOXY-PHENYLACETIC ACID was synthesised by nitrating m-cresole in position 2, then methylating it with dimethyl sulphate. The methyl ether was condensed with ethyl oxalate to 2-nitro-3-methoxy-phenylpyruvic acid, and this oxidised to the corresponding phenylacetic acid.



The chloride of the phenylacetic acid was condensed with homoveratrylamine to β-(3,4-dimethoxy-phenyl)-ethyl-2'-nitro-3'-methoxy-phenacetamide (I). Ring closure was obtained with PCl5 to the corresponding isoquinoline compound (II). The base was treated with methyl iodide (III) and then reduced with zinc and hydrochloric acid to the amino base(IV). By diazotation and subsequent heating the racemic alkaloid was obtained(V). It was resolved into its two optical forms with d- and l-tartaric acid.



(b) Experimental.

A. PREPARATION OF HOMOVERATRYLAMINE

1. Methylvanilline (45)

Vanilline (1 mol.) is melted in a wide-mouthed bottle provided with a condenser, a stirrer and two tap-funnels. With rapid stirring, 1.5 mol. KOH (82 g.) in 120 c.c. of water are run in at the rate of two drops a second and some moments later addition of 1.25 mol. (160 c.c.) of dimethyl sulphate is begun at the same rate. The external heating is soon stopped. The reaction mixture keeps a pale reddish-brown and alkaline. When three-fourths of the reagents have been added, the reaction mixture becomes turbid and separates in two layers. As soon as all has been run in, at the end of about 20 minutes, the mixture is poured into a porcelain basin. The upper layer solidifies to a hard white mass of practically pure methylvanilline. It is washed with water and dried.

In this way I obtained 354 g. of methylvanilline. Yield: 92.2%. m.p. 43-44°.

2. /

2. 3,4-Dimethoxycinnamic acid.[38]

Methylvanilline (300 g.) and malonic acid (400 g.) were dissolved in 1000 c.c. of pyridine and 18 c.c. of piperidine and heated for an hour on a steam bath. A rapid elimination of CO_2 took place and the reaction was completed by boiling the solution for 5 minutes. The product was cooled and poured into water acidified with 300 c.c. of concentrated hydrochloric acid. The cinnamic acid precipitates as long colourless needles, which, recrystallised from 30% alcohol, show a melting point of 180-181°.

Yield: 319 g. = 85% of theory.

3. 3,4-Dimethoxy-phenylpropionic acid.[40]

3,4-Dimethoxy-cinnamic acid (60 g.), dissolved in water (2000 c.c.) and sodium hydroxide (12 g.), was reduced with sodium amalgam (1700 g.) during one day and a half. The solution is kept only slightly alkaline by regular addition of dilute hydrochloric acid. When the reduction is finished, the solution is made just acid, then slightly alkaline again; some tar is precipitated, which is adsorbed by charcoal. The solution is filtered, cooled/

cooled and acidified. The propionic acid precipitates.

Long colourless needles from benzene, m.p. 97°.

Yield: 241 g. = 75% of theory.

4. 3,4-Dimethoxy-phenylpropionamide.(38)

Dimethoxy-phenylpropionic acid (220 g.) was dissolved in chloroform (530 c.c.) and thionyl chloride (174 g.) added. The mixture is left at room temperature for 12 hours, then heated to 40° for 2 hours. It is then poured carefully into a solution of sodium hydroxide (110 g.) in ammonia of d = 0.88 (2600 c.c.). The chloroform is distilled off in vacuo, the solution filtered from some tar and, on cooling, the amide precipitates. A further quantity of amide is obtained by extracting the filtrate with chloroform.

Short colourless needles from benzene m.p. 120-121°.

Yield: 157 g. = 71% of theory.

5. Homoveratrylamine.(41)

156 g. of phenylpropionamide were treated with sodium hypochlorite as follows: 3,4-dimethoxy-phenylpropionamide (26 g.) was added to an ice-cold solution/

solution in 10% sodium hydroxide (200 c.c.) of the chlorine produced by the reaction of hydrochloric acid (1:1) on potassium permanganate (6 g.). The flask was heated at first with the hand and then on the water bath. After an hour, during which temperature did not exceed 50°, some drops of the amine began to precipitate. The solution was cooled and caustic soda (75 g.) added. In order to precipitate all the amine, the solution was heated another 2 hours at 40°. After cooling, the amine was extracted three times with 30 c.c. ether, the ether dried with sodium sulphate. Gaseous hydrochloric acid was passed through the solution and the hydrochloride precipitated as a white crystalline mass, which is very hygroscopic, when not absolutely pure.
Needles from alcohol and ether m.p. 149-151°.
Yield: 95.5 g. = 63.7% of theory.

B. /

B. PREPARATION OF 2-NITRO-3-METHOXY-PHENYL-ACETIC ACID.

1. 2-Nitro-m-cresol. (42)

m-Cresol (200 g.), in two portions of 100 g. was dissolved in fuming sulphuric acid (8.3% SO_3) (370 c.c.) and the oily liquid cooled to +2°. A mixture of 43 c.c. fuming nitric acid (d = 1.5) in 100 c.c. of fuming sulphuric acid (8.3% SO_3) was run in drop by drop with vigorous stirring and the temperature kept below +5°. After one day at room temperature, water (200 c.c.) was added carefully and over-heated steam blown through, first at 110°, then at 150°. The nitro-m-cresol distils as a yellow butter-like mass, which is extracted with ether. The solution is dried and the ether evaporated. There remains a yellow-brown oil, which crystallises only after a long time in long needles. Yield: 203 g. = 71.5% of theory.

2. 2-Nitro-3-methoxy-toluene. (43)

1-Methyl-2-nitro-3-oxybenzol (153 g.) was mixed with anhydrous potassium carbonate (205 g.); the dark-orange potassium salt is formed with evolution of/

of heat. This salt was methylated during 10 hours in xylene (710 c.c.) with dimethyl sulphate (125 c.c.). The hard mass which forms on the bottom of the flask is crushed at frequent intervals with a glass rod. After 2 and 4 hours, another 30 c.c. of dimethyl sulphate are added. The orange colour disappears almost entirely. Steam is blown through the solution. Xylene is first recovered, then some m-methylanisol passes over and finally the methyl-ether. The volume of distilled water was approximately 11 litres. The ether crystallises in large hexagonal tablets, whereas the two other isomers remain liquid and can be separated.

Pale yellow hexagonal tablets: m.p. 54°.

Yield: 148 g. = 89% of theory.

3. 2-Nitro-3-methoxy-phenylpyruvic acid.(44)

Potassium metal (19.7 g.) was powdered under xylene, the latter decanted away and the potassium washed twice with absolute ether. Absolute ether (600 c.c.) was added and a mixture of absolute ethyl alcohol (28.2 c.c.) and absolute ether (25.8 c.c.) run in slowly enough to keep the ether from boiling too violently. After one hour a large quantity of sodium/

sodium ethylate had formed and ethyloxalate (73.5 g.) was added. The solution became deep yellow; it was cooled to 5° and 2-nitro-3-methoxy-methylbenzol (84 g.) dissolved in as little ether as possible, gradually added. The solution turns deep green and becomes red after a few minutes. The flask is fitted with a reflux condenser and kept for 20 hours at 37°. At the end of that time the potassium salt of the pyruvic acid has precipitated as a dark red cake, which is dissolved in water, separated from the ethereal layer, and washed twice with ether. The alkaline solution was acidified with hydrochloric acid and the pyruvic acid separated as a red oil, which solidified on cooling.

Yield: 79 g. = 66% of theory.

4. 2-Nitro-3-methoxy-phenylacetic acid.(44)

The crude pyruvic acid was dissolved in the minimum quantity of 2% sodium hydroxide and oxidised with 1300 c.c. of hydrogen peroxide (20 volumes).

Long pale yellow needles, m.p. 138°.

Yield of crude acid: 67.7 g. = 97% of theory.

Yield of recrystallised acid: 54.0 g.

C. /

C. SYNTHESIS OF THE ALKALOID.

1. Condensation of momoveratrylamine and 2-nitro-3-methoxy-phenylacetic acid.

2-Nitro-3-methoxy-phenylacetic acid (30 g.) was dissolved in chloroform (140 c.c.) and provided with thionyl chloride (95 c.c.). The mixture was allowed to react at room temperature for 24 hours; it was then heated 2 hours at 40° to complete the reaction. Chloroform and thionyl chloride were evaporated in vacuo and the chloride, which forms a dark-brown crystalline mass, left one day in vacuum over caustic potash.

On the other hand, homoveratrylamine-hydrochloride (31 g.) was decomposed with dilute caustic soda, dissolved in ether, the ether dried and distilled off. To the solution of the amine in dry benzene (400 c.c.) was added with vigorous shaking the solution of the phenylacetic chloride in as little benzene as possible. The mixture was allowed to stand for one hour and was shaken repeatedly. Then 1N. potassium hydroxide (145 c.c.) was added, in order to neutralise the hydrochloric acid formed in the reaction. Another 200 c.c. of benzene were added and the flask heated gently on the water bath until/

until all the amide dissolved. The benzolic layer was separated, washed with water, filtered and left to evaporate.

Yield: 35.0 g. = 66% of theory.

Faintly yellow long prisms from 30% methyl alcohol.

Analysis: 5.358 mg. gave 11.915 mg. CO_2 and 2.850 mg. H_2O

Found: 60.76% C; 5.96% H.

Calculated for $C_{18}H_{22}O_6N_2$: 60.93% C; 5.92% H.

4.018 mg. gave 0.267 c.c. N_2 at 747 mm/14°.

Found: 7.77% N.

Calculated for $C_{18}H_{22}O_6N_2$: 7.50% N.

2. 2'-nitro-3'-methoxy-3,4-dimethoxy-10-benzyl-7,8-dihydro-isoquinoline.

The amide described above (30 g.) was worked up in portions of 5 g. The amide (5 g.) was dissolved in chloroform (50 c.c.), cooled down under the water tap, and phosphorus pentachloride (6 g.) added in small portions. The flask was sealed and left at room temperature for 48 hours with frequent shaking. Chloroform and phosphorus oxychloride/

oxychloride were evaporated in vacuo and the remaining yellow cake heated for one hour under reduced pressure (18 mm.) at 50°. It was then extracted with boiling water (500 c.c.), the aqueous solution was filtered, and, after it had cooled down and had been made alkaline, extracted with ether. The solution was thoroughly dried and gaseous hydrochloric acid passed through it. The hydrochloride of the base precipitated as a crystalline mass of fine needles.

Colourless short needles from absolute alcohol, m.p. 222-223°.

Yield: 21.3 g. hydrochloride = 67.8% of theory.

Analysis: 3.753 mg. gave 7.970 mg. CO_2 and 1.748 mg. H_2O

Found: 57.92% C; 5.26% H.

Calculated for $C_{18}H_{21}O_5N_2Cl$: 58.01% C; 5.35% H.

When the pure hydrochloride is decomposed and the base dissolved in ether, the ether being left to evaporate slowly, the isoqninoline base crystallises in large beautiful rhombs melting at 129-130°.

3. /

3. Methiodide of the isoquinoline base.

The hydrochloride of the isoquinoline compound was decomposed and the free base (19.4 g.) refluxed for 2 hours with methyl iodide (70 c.c.). The methiodide precipitates and is filtered from the remaining methyl iodide. To remove some unchanged base and some impurities, it is extracted for 24 hours with absolute ether in a Soxhlet extractor.

Yield: 26.8 g. = 98.5% theory.

Long yellow needles from water. m.p. 222-223°.

Analysis: 5.928 mg. gave 0.299 c.c. N_2 at 735 mm./10°.

Found: 5.88% N.

Calculated for $C_{20}H_{23}O_5N_2I$: 5.62% N.

4. 2'-Amino-3'-Methoxy-3,4-dimethoxy-9-methyl-10-benzyl-tetrahydroisoquinoline.

The methiodide (26.8 g.) is dissolved in 270 c.c. concentrated hydrochloric acid and 270 c.c. water and gently heated on the water bath. During half an hour, zinc dust (82 g.) is added while the contents of the flask are well stirred. The solution becomes nearly colourless.

When the reduction is finished, the solution is/

is extracted six times with ether and then made strongly alkaline, so as to dissolve the zinc as sodium zincate. The amino base is dissolved in ether, this extracted with dilute hydrochloric acid and the amine redissolved in ether. The solvent is distilled off, and the amine dissolved in chloroform. Hydrochloric acid gas is led through and the dihydrochloride precipitates as a green pasty mass. Petrol ether (80-100°) is added carefully to precipitate the dihydrochloride, and the flask is cooled in the ice box for a night. The crystalline salt, which has a dirty grey colour, is digested three times with acetone and becomes almost colourless.

Yield: 14.8 g. = 66% of theory.

Small prisms from absolute alcohol and ether m.p. 217-218°.

Analysis: 4.770 mg. gave 10.105 mg. CO_2 and 2.980 H_2O.

Found: 57.77% C; 6.98% H.

Calculated for $C_{20}H_{28}O_3N_2Cl_2$: 57.83% C; 6.80% H.

8.102 mg. gave 5.620 mg. AgCl.

Found: 17.15% Cl. Calculated 17.10% Cl.

5./

5. Racemic alkaloid.

The hydrochloride of the amino base (14.6 g.) was dissolved in 75 c.c. of methyl alcohol and 75 c.c. of 2N. sulphuric acid. It was diazotised with the equivalent of 0.5N. $NaNO_2$. The solution becomes dark red. It was then allowed to warm up very slowly; nitrogen escapes and ring closure takes place to the phenanthrene derivative.

In order to reduce any dihydroisoquinoline base to tetrahydroquinoline, the solution is reduced during half an hour with 22 c.c. of concentrated hydrochloric acid and 11 g. of zinc dust. The solution is diluted while still hot with 200 c.c. of water, and some tarry substance précipitates. The base is extracted with ether, then retaken in dilute hydrochloric acid, again in ether. The ether is extracted with a minimum quantity of dilute acid, the solution made almost neutral with ammonia and a great excess of concentrated potassium iodide solution poured in.

The hydriodide precipitates as a brownish, crystalline mass. It can be recrystallised from absolute methyl alcohol and ether; it is excessively soluble in water.
Small tablets, colourless at first, finally becoming slightly brown. m.p. 249-250°.

Analysis/

Analysis: 4.128 mg. gave 8.049 mg. CO_2 and 2.045 mg. H_2O

Found: 53.17% C; 5.54% H.

Calculated for
$C_{20}H_{24}O_3N$ I: 53.00% C; 5.29% H.

6. Resolution

The racemic alkaloid (1.52 g.) was dissolved in absolute alcohol (27 c.c.), heated to 40° and to this solution was given a solution of d-tartaric acid (0.82 g.) in absolute alcohol (40 c.c.). If a smaller quantity of alcohol is used and the tartrate left to crystallise on cooling, it always precipitates out pasty. On the contrary, I have found that I could obtain the tartrate in a fairly pure state if an excess of alcohol was used at the beginning and then evaporated in vacuo.

Little prisms from methyl alcohol and ether. m.p. 223-224°.

Analysis: 4.035 mg. gave 8.673 mg. CO_2 and 2.111 mg. H_2O.

Found: 58.62% C; 5.85% H.

Calculated for
$C_{24}H_{28}O_9N$: 58.54% C; 6.43% H.

Rotation in water:

$[\alpha] = -5.52°$; L = 2; c = 1.941; T = 16°.

$[\alpha] = -138.2°$

The/

The pure l-alkaloid-d-tartrate was decomposed and the free base obtained. It did not crystallise; its hydrochloride (thick needles) melted at 189-190°.

Rotation in absolute alcohol: (base)

$[\alpha] = -10.4°$; L = 2; c = 2.060; T = +17°

$$[\alpha]_D^{17} = -252.4°$$

The mother liquors of the filtration of the l-alkaloid-d-tartrate are collected, the alcohol distilled away in vacuo. The base is taken in ether and the red oil which remains after the distillation of the ether (0.312 g.) is dissolved in absolute alcohol (5 c.c.) and a solution of l-tartaric acid (0.170 g.) in absolute alcohol (8 c.c.) added.

The d-alkaloid-l-tartrate which has precipitated, is recrystallised from methyl alcohol and ether.

Little prisms. m.p. 218-219°.

Rotation in water:

$[\alpha] = +5.70°$; L = 2; c = 2.023; T = 16°

$$[\alpha]_D^{16} = +140.8°$$

The/

The pure d-alkaloid-l-tartrate was decomposed and the free base obtained: it could not be obtained in crystalline form. m.p. of hydrochloride: 188-189°.

Rotation in absolute alcohol. (base)

$[\alpha] = +9.95°$; L = 2; c = 1.958; T = +17°.

$$[\alpha]_D^{17} = +254.1°$$

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